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Calyciphylline B-type Alkaloids: Evolution of a Synthetic Strategy to (−)-Daphlongamine H

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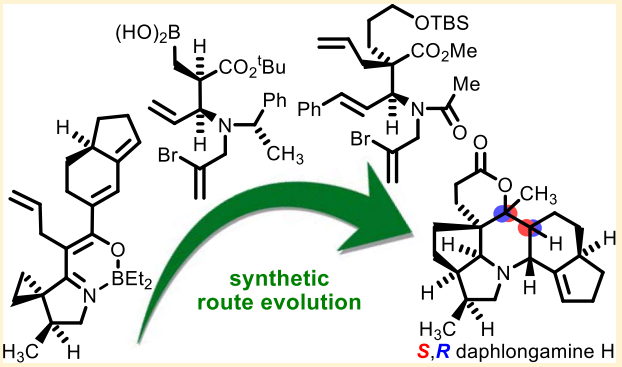
Supporting Information

ABSTRACT: We provide a full account of our synthetic studies targeting the hexacyclic calyciphylline B-type alkaloids, a subfamily of the *Daphniphyllum* natural products. Following an initial set of synthetic strategies focused on constructing the piperidine core of the calyciphylline B-type framework via a 6π-azaelectrocyclization, as well as exploiting the reactivity of underexplored oxazaborinine heterocycles, we ultimately designed a highly functionalized acyclic precursor which underwent carefully orchestrated and efficient cyclizations to forge the architecturally complex natural product scaffold. Our efforts have culminated in the development of the first total synthesis of (−)-daphlongamine H, provided access to its C5-epimer, (−)-isodaphlongamine H, and led to structural revision of deoxyisocalyciphylline B.



INTRODUCTION

The *Daphniphyllum* alkaloids are a large family of natural products which exhibit a wide range of intriguing biological activities, such as antioxidant and anticancer properties, as well as promotion of nerve growth factor production.[1] By virtue of this pharmacological potential and the highly diverse and complex azapolycyclic architectures of these compounds, they have emerged as important total synthesis targets.[2] Following seminal work by Heathcock and co-workers on the secodaphniphylline subset of these alkaloids,[3] intense synthetic efforts toward various other *Daphniphyllum* alkaloids were also reported (Figure 1a). In the past decade, chemists have been especially enticed by calyciphylline A-type and daphmanidin A-type alkaloids, and elegant total syntheses of natural products within this family were reported by the groups of Carreira,[4] Li,[5] Smith,[6] Fukuyama,[7] Dixon,[8] Zhai,[9] Qiu,[10] Xu,[11a] and Gao.[12] Recently, Xu and co-workers also completed total syntheses of both a daphnezomine A-type[11b] and bukittinggine-type alkaloid.[11c]

Calyciphylline B-type compounds belong to a small, structurally distinct subclass among the 320 known *Daphniphyllum* alkaloids (Figure 1b). These secondary metabolites feature a unique hexacyclic framework (rings A−F) containing a central tertiary amine that is surrounded by seven contiguous stereocenters. Following the discovery of the *N*-oxide parent member, calyciphylline B,[13] deoxycalyciphylline B (**1**),[14] and related congeners with differing C5/C6 configurations, such as daphlongamine H (**2**),[15] were isolated. In addition, two calyciphylline B-type alkaloids with oxygenated E rings (**4**−**5**),[16] as well as two derivatives where the labile δ-lactone moiety has undergone methanolysis, have been reported (**6**−**7**).[17] Biosynthetically, it is proposed that precursor A (Figure 1c), containing a tetrasubstituted olefin (ΔC5−C6) and appended propionic acid side chain, might undergo non-selective hydroacyloxylation to give four diastereomeric lactone products.[14,18] In this regard, Hanessian and co-workers reported an elegant total synthesis of isodaphlongamine H (**3**)[19] and hypothesized that this compound was a "missing" diastereomeric congener of the calyciphylline B-type alkaloids, which had yet to be isolated from natural sources. Recently, we accomplished the first total synthesis of (−)-daphlongamine H (**2**)[20] and revised the reported *S*-C6 configuration of deoxyisocalyciphylline B to *R*-C6, thus revealing that (−)-daphlongamine H (**2**) and isolated deoxyisocalyciphylline B (**2′**) are effectively the same natural product. For the calyciphylline B-type alkaloids (**1**−**7**), and on the basis of our structural revision, only the natural occurrence of deoxycalyciphylline B (**1**) and daphlongamine H (**2**) has been unambiguously confirmed to date.

Compared to numerous other synthetic studies focusing on *Daphniphyllum* alkaloids such as the calyciphylline A-type alkaloids, the calyciphylline B-type subfamily has attracted relatively little attention from the synthetic community.[2b] Prior to and during the period of our own endeavor, the groups of Hanessian and Bélanger reported their synthetic studies on the calyciphylline B-type alkaloids. Their strategies to access the western tricyclic substructure are highlighted in Scheme 1. As part of their studies, Hanessian and co-workers demonstrated the convergent enolate alkylation of β-ketoester **8** with chiral

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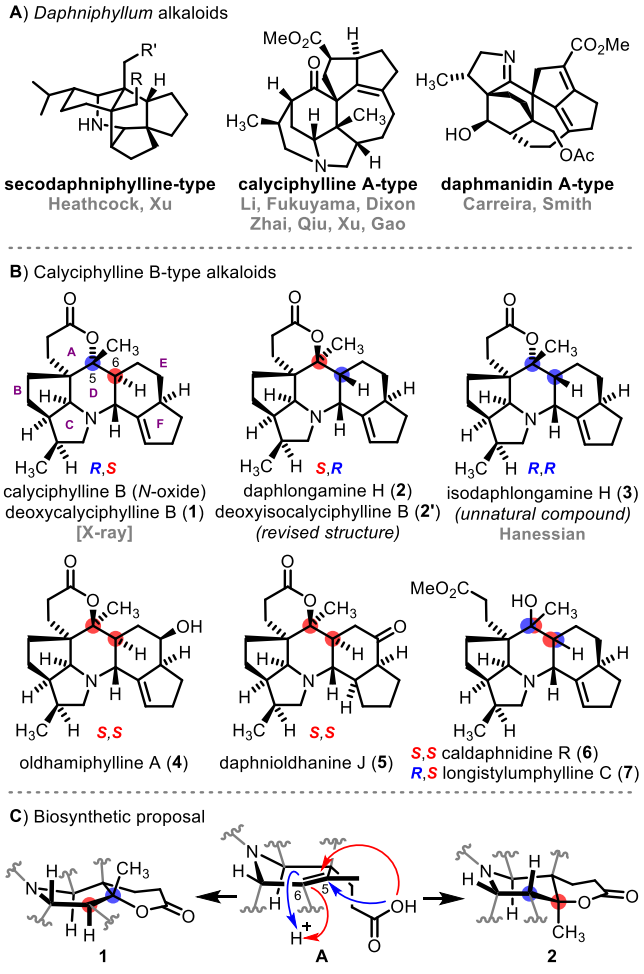
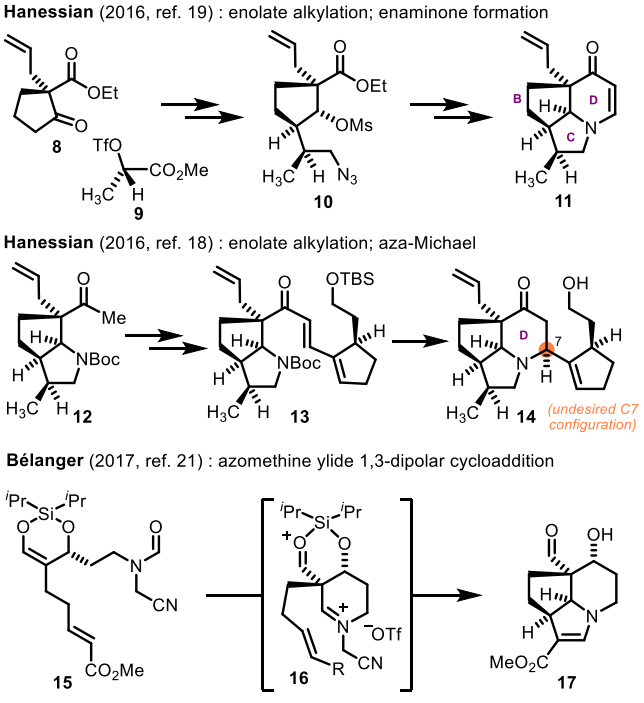


Figure 1. Calyciphylline B-type alkaloid subfamily.

Scheme 1. Previous Approaches to the Tricyclic Core of the Calyciphylline B-type Alkaloids



triflate **9**.[19] The resulting adduct was then elaborated to azide **10**, which upon reduction to an amine group underwent mesylate displacement to give the pyrollidine C ring. The enaminone D ring of tricycle **11** was finally forged by a 1,4-addition of the secondary amine onto a pre-installed ynone moiety. The latter compound served as a key intermediate in their elegant total synthesis of isodaphlongamine H (**3**). The same group also reported detailed synthetic and computational studies of their previous unsuccessful approaches. This insightful report was particularly revealing in terms of the challenges and difficulties encountered with respect to the installation of the desired C7 stereochemistry.[18] Ketone **12** was converted to dienone **13**, which underwent an aza-Michael addition to form the piperidine D ring in **14**, albeit bearing the opposite C7 configuration relative to the one found in the naturally occurring calyciphylline B-type alkaloids.

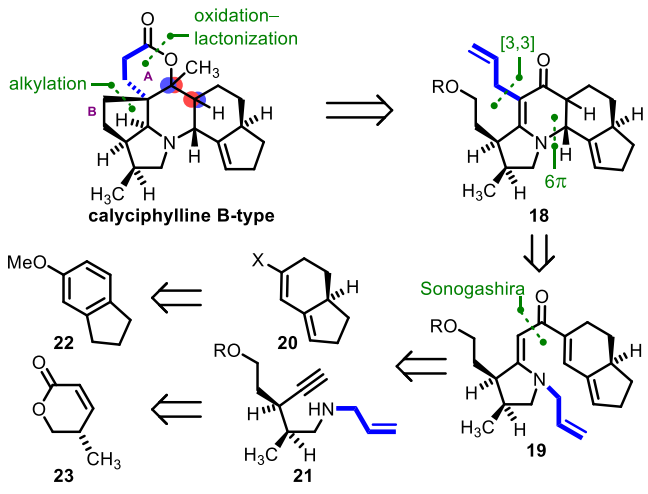
Bélanger and co-workers have also reported creative synthetic studies toward the western tricyclic substructure of the calyciphylline B-type alkaloids. Their approach involved preparation of cyclic silyl enol ether **15**, which was elaborated to tricyclic core structure **17** through a 1,3-dipolar cycloaddition of an in situ generated azomethine ylide via iminium ion **16**.[21] While tricyclic core structure **17** was constructed efficiently in this way, numerous redox manipulations appear necessary to advance it to the calyciphylline B-type alkaloids.

Fascinated by the beautiful yet daunting architectures of the calyciphylline B-type alkaloids, we also embarked on a synthesis of these compounds. Herein, we disclose full details of our synthetic journey that culminated in the first total synthesis of (−)-daphlongamine H (**2**), gave access to its C5-epimer, (−)-isodaphlongamine H (**3**), and led to a structural revision of deoxyisocalyciphylline B (**2′**). We particularly highlight how several initial approaches led to interesting discoveries and insights that ultimately enabled an efficient and successful synthetic route to construct the calyciphylline B-type architecture.

RESULTS AND DISCUSSION

Initial Strategy. In an early synthetic plan (Scheme 2), it was envisioned that the lactone and cyclopentane (rings A and B) of the calyciphylline B-type alkaloids could be constructed at a final stage from tetracyclic enaminone **18** via oxidation–lactonization of the appended allyl group and an intra-

Scheme 2. Initial Retrosynthetic Analysis



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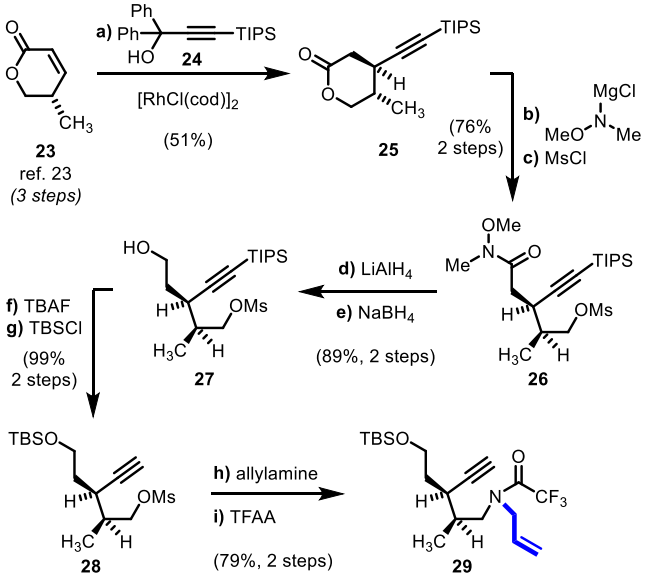
molecular alkylation reaction, respectively. A central feature of this retrosynthetic plan would involve assembly of **18** via an ambitious cascade process. Specifically, in the forward sense, we were enticed by the prospect of a suitable activation of precursor *N*-allyl vinylogous amide **19**, which would induce a sequence entailing a formal [3,3] sigmatropic rearrangement and a 6π-azaelectrocyclization[22] to forge tetracyclic enaminone **18**. Given the scant literature precedent associated with this planned cascade, we reasoned that the sequence might at the very least also be executable in a stepwise manner. *N*-Allyl vinylogous amide **19** was traced back to hydro-indene **20** and alkyne **21** as reactants for a convergent union through Sonogashira coupling. In turn, enantiomerically enriched **20** would be derived from 5-methoxyindane (**22**), while **21** could be obtained via elaboration of known α,β-unsaturated lactone **23**.[23]

As outlined in Scheme 3, preparation of alkyne **29** began with conjugate addition of an acetylide equivalent to α,β-unsaturated lactone **23**. While copper and aluminum acetylides failed to undergo this desired transformation, the Rh-catalyzed method introduced by Hayashi,[24] using silanol **24** to generate a rhodium acetylide species in situ, proved successful in furnishing disubstituted lactone **25** in 51% yield. The latter compound was then subjected to Weinreb amide formation to provide a primary alcohol which upon mesylation furnished **26**. Following a two-step reduction, alcohol **27** was obtained in 89% yield. This more lengthy synthetic sequence was adopted because the initially planned direct conversion of disubstituted lactone **25** to alcohol **27**, via reduction and subsequent differentiation of the two primary hydroxy groups, did not proceed with satisfactory selectivity. Next, protecting group manipulations gave silyl ether **28** which readily underwent mesylate displacement with allylamine to give an intermediate, unstable, secondary amine that was converted to trifluoroacetyl protected alkyne **29**.

Scheme 3. Synthesis of Alkyne 29[a]

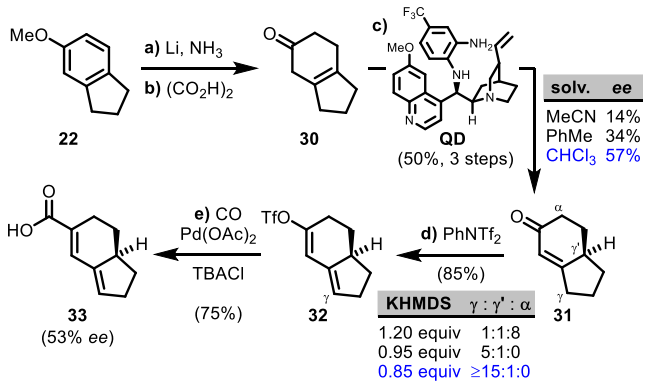


[a]Reagents and conditions: (a) **24**, $[RhCl(cod)]_2$, Cs_2CO_3, PhMe, 80 °C (51%); (b) Me(OMe)NH·HCl, ^{i}PrMgCl, THF, 0 °C; (c) MsCl, NEt_3, CH_2Cl_2, 0 °C (76%, 2 steps); (d) $LiAlH_4$, THF, 0 °C; (e) $NaBH_4$, CH_2Cl_2, MeOH, 0 °C (89%, 2 steps); (f) TBAF, THF, 0 °C; (g) TBSCl, imidazole, CH_2Cl_2, 0 °C (99%, 2 steps); (h) allylamine, NaI, NEt_3, MeCN, 45 °C; (i) TFAA, NEt_3, CH_2Cl_2, −78 °C (79%, 2 steps). TIPS = triisopropylsilyl, THF = tetrahydrofuran, cod = 1,5-cyclooctadiene, Ms = CH_3SO_2, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TFAA = trifluoroacetic anhydride.

For the synthesis of the enantiomerically enriched hydro-indene substructure (EF rings), we explored Birch reduction of anisole **22** (Scheme 4) followed by mild hydrolysis of the resulting enol ether[25] to give β,γ-unsaturated ketone **30**. According to Deng's method for the enantioselective isomerization by cooperative iminium-base catalysis,[26] **30** was treated with cinchona alkaloid-derived organocatalyst **QD** to give enone **31**. The best selectivity in this transformation was achieved by addition of (*R*)-2-chloropropionic acid as a co-catalyst and use of chloroform as the solvent. Even though the optical purity of enone **31** remained mediocre (57% ee) despite our optimization attempts,[27] we reasoned that it would suffice for our preliminary studies. Particularly, because the hydro-indene bicycle would be combined with an enantiomerically pure building block (i.e., alkyne **29**), a resolution would be achieved at a later stage. The subsequent preparation of γ-dienol triflate **32** from enone **31** proved nontrivial because of an accompanying erosion of optical purity, as well as the competing formation of undesired and inseparable α- and γ'-dienol triflate isomers. A thorough investigation of various enolization conditions finally revealed that employing a substoichiometric amount of KHMDS enabled the selective generation of dienol triflate **32**.[27] It is hypothesized that under these optimized reaction conditions, the kinetic α-dienolate equilibrates to the desired γ-dienolate prior to triflation.

Palladium-catalyzed carbonylation,[28] followed by hydrolysis of the intermediate acid chloride, then provided carboxylic acid **33** in 75% yield. At this stage, chiral HPLC analysis of **33** (53% ee) confirmed that only minimal erosion of optical purity had taken place in the preceding, optimized triflation of enone **31**.[29]

Scheme 4. Synthesis of Enantiomerically Enriched Carboxylic Acid 33[a]



[a]Reagents and conditions: (a) Li, NH_3 (l), THF, −78 to −40 °C, then EtOH, −40 to 23 °C; (b) oxalic acid, MeOH, H_2O, 0 °C; (c) **QD** (15 mol %), (*R*)-2-chloropropionic acid (30 mol %), $CHCl_3$, −20 °C (50%, 57% ee); (d) KHMDS, THF, −15 to 23 °C, then $PhNTf_2$, 0 °C (85%); (e) CO (g), $Pd(OAc)_2$, TBACl, pyridine, DMF, 60 °C (75%, 53% ee). KHMDS = potassium bis(trimethylsilyl)amide, Tf = CF_3SO_2, TBACl = tetrabutylammonium chloride, DMF = *N*,*N*-dimethylformamide.

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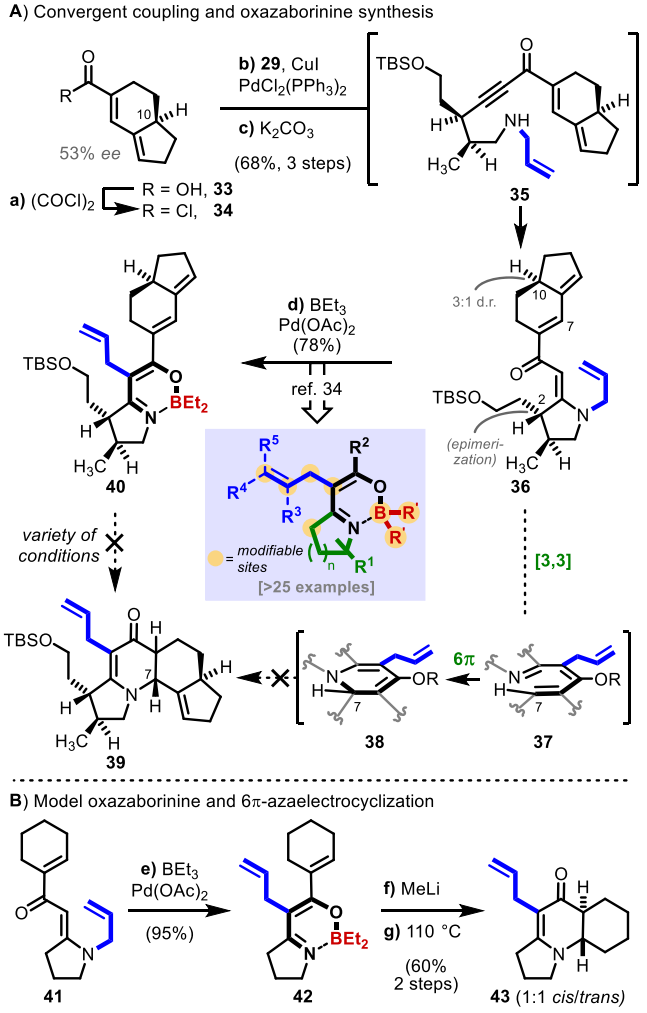
Having secured access to both building blocks for the convergent coupling, the synthesis of the key step precursor (cf. **19**, Scheme 2) was pursued (Scheme 5a). To this end,

Scheme 5. Synthesis of Oxazaborinine 40 and Attempted Key Cascade Reaction[a]



[a]Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 to 23 °C; (b) **29**, CuI, $PdCl_2(PPh_3)_2$, NEt_3, 23 °C; (c) K_2CO_3, MeOH, THF, H_2O, 23 °C (68%, 3 steps, 3:1 d.r. at C10); (d) BEt_3, $Pd(OAc)_2$, PPh_3, PPTS, PhMe, 80 °C (78%, 3:1 d.r. at C10); (e) BEt_3, $Pd(OAc)_2$, PPh_3, PPTS, PhMe, 80 °C (95%); (f) MeLi, THF, −78 to 0 °C (70%); (g) TBSCl, NEt_3, PhMe, 110 °C (42% *trans*-**43**; 44% *cis*-**43**). PPTS = pyridinium *p*-toluenesulfonate.

carboxylic acid **33** was converted to the corresponding acid chloride (**34**) and subjected to Sonogashira coupling with alkyne **29**.[30] The intermediate alkynone was treated with K_2CO_3 in methanol to remove the trifluoroacetate group and reveal the secondary amine (**35**) which underwent aza-Michael addition to give *N*-allyl vinylogous amide **36**. The latter compound features the nor-carbon framework of all calyciphylline B-type alkaloids and was obtained as an inseparable mixture of diastereomers (~3:1 d.r. at C10), as a result of the mediocre enantiomeric purity of coupling partner **34**. Unexpectedly, NMR analysis (NOESY) of vinylogous amide **36** revealed that the C2 stereocenter had inverted after the aza-Michael reaction to give the resulting pyrrolidine substructure bearing *trans*-disposed substituents. We were unable to avoid this spontaneous and thermodynamically favored epimerization, which readily took place as it alleviates steric strain induced by the *syn*-orientation of the substituents. Cognizant that the undesired C2 configuration of **36** would have to be corrected at a later stage—a transformation which we believed should be achievable by kinetic γ-deprotonation and protonation—we aimed to identify suitable activation of *N*-allyl vinylogous amide **36** to forge tetracyclic enaminone **39** via the formal [3,3] rearrangement and 6π-azaelectrocyclization (cf. **37** and **38**). Initially focusing on the first step of this ambitious key cascade, it was soon established that the planned [3,3] sigmatropic rearrangement was challenging. This circumstance was further corroborated by very limited existing literature precedent for the formal [3,3] rearrangement of *N*-allylic enaminones,[31] in contrast to the related aza-Claisen variant involving enamine substrates.[32,33] After careful experimentation, we were pleased to discover that treatment of *N*-allyl vinylogous amide **36** with the specific combination of triethylborane, palladium(II) acetate, triphenylphosphine, and pyridinium *p*-toluenesulfonate gave rise to the [3,3] rearranged product which was isolated as the corresponding oxazaborinine **40** in 78% yield. At this stage, we recognized the utility of this powerful and highly efficient transition-metal-catalyzed oxazaborinine synthesis and devised an independent methodology to explore the scope of this novel discovery.[34] While oxazaborinines are valuable structural motifs that have found applications in research ranging from materials chemistry[35] to pharmaceutical development,[36,37] we were especially interested in investigating the unique and underexplored reactivity of these boron heterocycles for use in complex molecule synthesis. For example, the oxazaborinine moiety can serve as a remarkably stable protecting group for the vinylogous amide and can be removed with organolithium reagents or by treatment with aqueous acid.

As outlined in Scheme 5b, model oxazaborinine **42** was converted to tricycle **43** via cleavage of the boron heterocycle to reveal the vinylogous amide that underwent 6π-azaelectrocyclization at elevated temperature.[29] Disappointingly, translation of this reaction sequence to the conversion of oxazaborinine **40** to the desired tetracyclic enaminone (**39**) proved unsuccessful (Scheme 5a). Hydrolysis of the boron heterocycle in **40** under a variety of conditions gave rise to only trace amounts of the corresponding α-allyl vinylogous amide and mostly resulted in complex product mixtures and nonspecific decomposition.

Modified Oxazaborinine Approach. Our ability to assemble a model system of the calyciphylline B-type alkaloid core (i.e., **43**), by means of a formal [3,3] rearrangement and a subsequent 6π-azaelectrocyclization, convinced us that this conceptual strategy was worth further pursuit. However, at this juncture, we envisioned a modified synthetic sequence that would avoid the problematic epimerization of the C2 stereocenter and also allow us to exploit the unique reactivity of the oxazaborinine heterocycle for constructing the calyciphylline B-type core structure (Scheme 6). While the endgame disconnection for the lactone moiety would remain identical, a diastereoselective reduction of pentacyclic enamine **44** was envisioned to give the all-*cis* substituted pyrrolidine substructure. We considered two distinct strategies to access **44** from either enaminone **45** or haloimine **46**, both of which could arise from cyclopropyl oxazaborinine **47**. In the former pathway, the B ring of **44** would result from a vinylcyclopropane rearrangement (VCPR)[38] of enaminone **45**,

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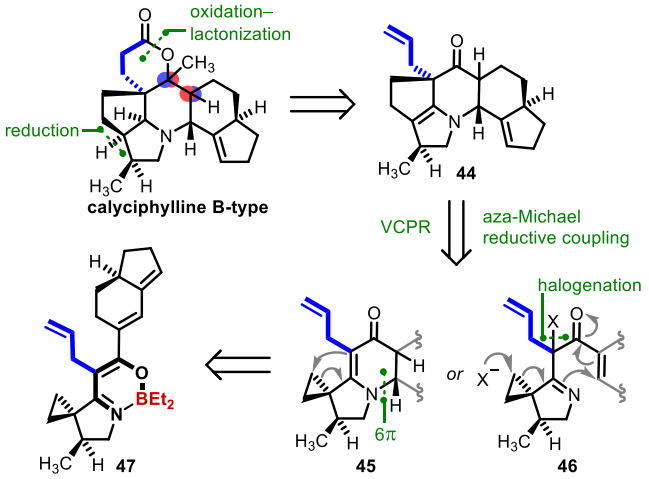
Scheme 6. Revised Retrosynthesis Using Cyclopropyl Oxazaborinine 47

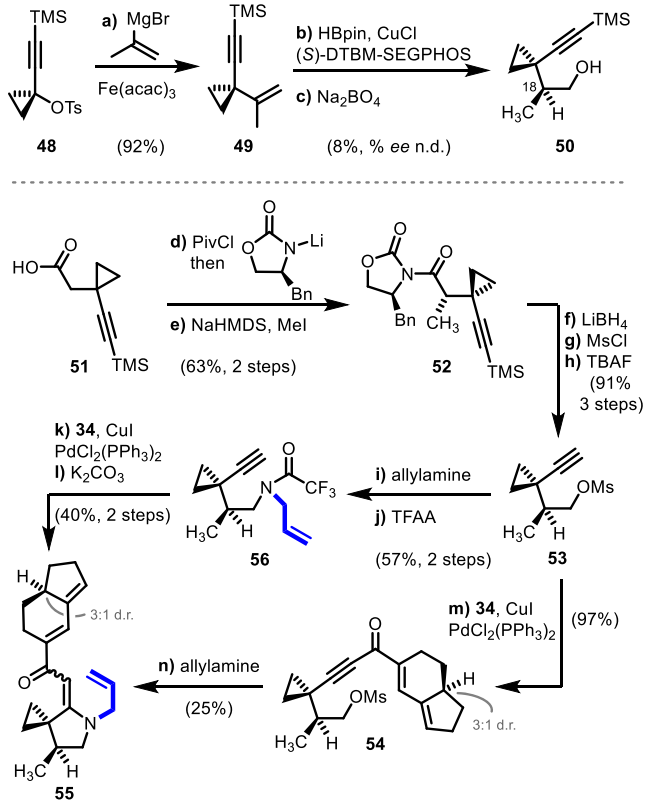


itself being derived from **47** via the established hydrolysis and 6π-azaelectrocyclization sequence. It was postulated that the activated nature of the system would enable the VCPR in **45** under significantly milder conditions compared to the classical variant,[39] which often requires temperatures exceeding 350 °C. With the advent of methods for C−C activation in strained ring systems,[40] we anticipated that a formal VCPR might also be feasible by employing transition-metal catalysis. With respect to the alternative pathway, the central ring of pentacyclic enamine **44** would be forged from haloimine **46** through halide ring opening of the activated cyclopropane,[41] an aza Michael reaction, and reductive coupling of the resulting dihalide.[42] We anticipated utilizing the established conditions for α-halogenation of oxazaborinines to access haloimine **46**.[34]

The synthesis of cyclopropane containing oxazaborinine **47** began with preparation of a new alkyne Sonogashira coupling partner (Scheme 7). Initially, we attempted to install the C18 stereocenter using an enantioselective hydroboration[43] of alkene **49** to give alcohol **50** following oxidation of the intermediate pinacolboronate. While the synthesis of alkene **49** from tosylate **48** was efficient using Fürstner's iron-catalyzed cross-coupling protocol for *tert*-alkyl electrophiles,[44] the subsequent hydroboration−oxidation was very low yielding.[29] Therefore, we turned instead to an auxiliary-based approach and prepared cyclopropyl acid **51** for an ensuing Evan's asymmetric enolate alkylation to give oxazolidinone **52**.[45] Following reduction of the imide, mesylation of the resulting primary hydroxy group and removal of the trimethylsilyl group gave alkyne **53** which underwent coupling with acid chloride **34** to furnish alkynone **54** in 97% yield. Displacement of the mesylate with allyl amine, followed by aza-Michael reaction, delivered the cyclopropyl containing vinylogous amide **55** in low yield together with numerous unidentified side products. Alternatively, cyclopropyl vinylogous amide **55** was accessed via amide **56**. However, **55** was obtained in comparable overall yield through the latter route, and we concluded that the product itself was somewhat unstable. Nevertheless, we were able to acquire sufficient quantities of **55** to begin investigating the key step.

Subjecting cyclopropyl vinylogous amide **55** to the established conditions for oxazaborinine synthesis gave **47** in 60% yield (Scheme 8). Presumably, as a result of the increased steric congestion at the γ-quaternary center in this substrate,

Scheme 7. Synthesis of Cyclopropyl Vinylogous Amide 55[a]



[a]Reagents and conditions: (a) $H_2C{=}C(CH_3)MgBr$, $Fe(acac)_3$, THF, −30 °C (92%); (b) HBpin, CuCl, KO^{t}Bu, (*S*)-(+)-5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole, PhMe, 23 °C; (c) Na_2BO_4, THF, H_2O, 23 °C (9%); (d) PivCl, NEt_3, THF, −78 to 0 °C then (premixed) *n*-BuLi, (*S*)-4-benzyl-2-oxazolidinone, −78 to 23 °C (80%); (e) NaHMDS, MeI, THF, −78 to 0 °C (79%); (f) $LiBH_4$, THF, MeOH, 0 °C (95%); (g) MsCl, NEt_3, CH_2Cl_2, 0 °C; (h) TBAF, THF, 0 °C (96%, 2 steps); (i) allylamine, NaI, NEt_3, MeCN, 45 °C; (j) TFAA, NEt_3, CH_2Cl_2, −78 °C (57%, 2 steps); (k) **34**, CuI, $PdCl_2(PPh_3)_2$, NEt_3, 23 °C; (l) K_2CO_3, MeOH, THF, H_2O, 23 °C (40%, 2 steps, 3:1 d.r. at C10); (m) **34**, CuI, $PdCl_2(PPh_3)_2$, NEt_3, 23 °C (97%, 3:1 d.r. at C10); (n) allylamine, NEt_3, MeCN, 60 °C (25%, 3:1 d.r. at C10). acac = acetylacetone, pin = pinacol, Piv = $(CH_3)_3CO$, NaHMDS = sodium bis(trimethylsilyl)amide.

the transformation was accompanied by formation of some deallylated oxazaborinine side product (10−20%).[34] Pursuing our plan to use an α-haloimine intermediate for construction of pentacyclic enamine **44** (cf. **46** in Scheme 6), conversion of cyclopropyl oxazaborinine **47** to haloimine **57** was attempted. Unfortunately, under various conditions (e.g., NCS; NBS; PIFA; and TMSCl), the masked boron enolate in **47** failed to undergo the desired α-halogenation and either unreacted starting material was recovered or nonspecific decomposition took place. We thus turned our attention to the envisioned VCPR and 6π-azaelectrocyclization sequence, and after considerable experimentation discovered that oxazaborinine **47** could be hydrolyzed in boiling ethanol in the presence of DMAP. Activation of the resulting α-allyl vinylogous amide at elevated temperature with a mild Lewis acid led to formation of a cyclized product with the desired N−C7 bond. Yet to our frustration, closer NMR analysis revealed that the product of the 6π-azaelectrocyclization had undergone spontaneous oxidation to give 4-pyridone **58**. Recognizing that the

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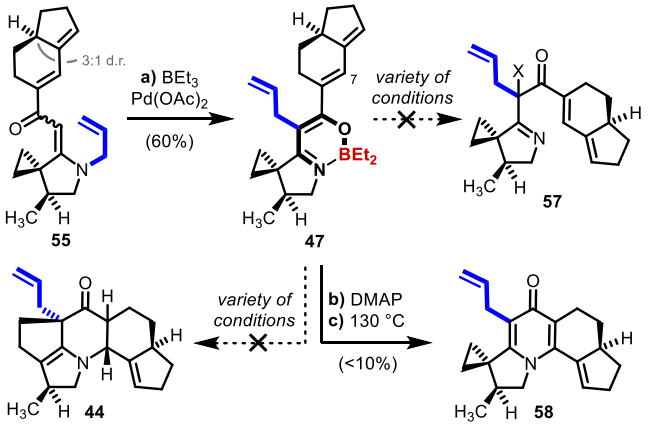
Scheme 8. Synthesis of Cyclopropyl Oxazaborinine 47 and Attempted Conversion to Pentacyclic Enamine 44[a]



[a]Reagents and conditions: (a) BEt_3, $Pd(OAc)_2$, PPh_3, PPTS, PhMe, 80 °C (60%, 3:1 d.r. at C10); (b) DMAP, EtOH, 80 °C; (c) *N,O*-bis(trimethylsilyl)acetamide, DMF, 130 °C (10%, 2 steps, 1.5:1 d.r. at C10).

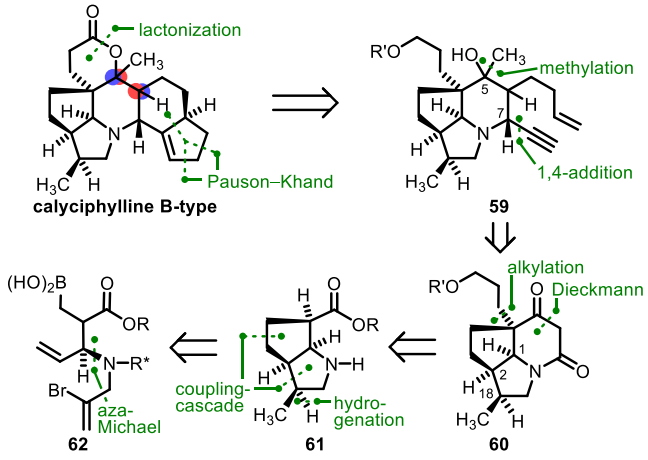
undesired oxidation of the dihydropyridone intermediate might be challenging to avoid under the harsh conditions required for the 6π-azaelectrocyclization, we attempted to carry out the VCPR prior to formation of the N−C7 bond.

Disappointingly, the VCPR could not be induced in neither **55** nor **47** under a variety of thermal, photochemical, Lewis acid [e.g., Et_2AlCl, MgI_2, $BF_3{\cdot}Et_2O$, $CuBr_2$, $Zn(OTf)_2$, $Yb(OTf)_3$] or transition-metal (Rh, Ni, Pd)-based activation methods.

New Strategy. In light of the difficulties encountered in attempting to form the key N−C7 bond in our oxazaborinine approaches, we began contemplating an entirely different synthetic strategy. At this stage, we also decided to abandon the convergent fragment coupling concept, as efficient installation of the remote C10 stereocenter in the hydroindene building block could not be achieved, and its use in mediocre enantiomeric purity had proven unsatisfactory. In the new route design, particular emphasis was placed on concise construction of the synthetically challenging, western all-*cis* 1-H/2-H/18-H substructure. With this in mind, the calyciphylline B-type framework was traced back to enyne **59** as the precursor for forming the hydro-indene substructure via a late-stage Pauson−Khand reaction (Scheme 9). In turn, tricycle **60** would constitute a key intermediate of the synthetic route, wherein the piperidinedione motif, readily derived from bicycle **61** via Dieckmann condensation, would serve as a versatile handle for installation of the C5−C7 substituents. We envisioned the all-*cis* methine substructure in **61** to result from an intramolecular Heck−Suzuki coupling cascade and diastereoselective hydrogenation. Thus, **61** was traced back to bifunctional β-amino ester **62** that contains the retron for an asymmetric aza-Michael reaction.

While a range of homochiral lithium amides derived from α-methylbenzylamine have been reported to undergo diastereoselective conjugate addition to α,β-unsaturated esters,[46] it was unclear at the outset of our investigations whether a sensitive vinyl bromide moiety in the lithium amide would be tolerated (Scheme 10). Fortunately, the conjugate addition of the lithium amide derived from **63** to pentadienoate **64** was rendered successful at low temperature along with careful control of the reaction time. These conditions proved critical

Scheme 9. Retrosynthetic Analysis of the Calyciphylline B-type Framework Based on Key Tricycle 60



in avoiding β-elimination of the vinyl bromide to give undesired propargylamine side products.[47] Next, β-amino ester **65** was α-methylenated in one pot by sequential alkylation and elimination to furnish enoate **66**. Before investigating the planned Heck−Suzuki cascade, we also explored if, albeit typically disfavored,[48] a 5-*exo*-trig/5-*endo*-trig sequence might allow direct conversion of enoate **66** to a bicyclic substructure reminiscent of **70**. However, the desired transformation could not be achieved under radical or Heck-type conditions.[49] Returning to the original plan, **66** was subjected to copper-catalyzed β-borylation, according to Molander's protocol,[50] to furnish boronic acid **67**, which was treated with a catalytic amount of $Pd(PPh_3)_4$ and aqueous Na_2CO_3 in tetrahydrofuran (THF) at elevated temperature. Although successful, the ensuing Heck−Suzuki cascade frustratingly gave rise to *trans*-bicycle **70** and trace amounts of the corresponding C8 epimer,[29] without detection of any of the desired *cis*-bicycle. The stereochemical outcome of this transformation had been difficult to deduce with certainty, given the multitude of rotational isomers of precursor **67**. In retrospect, we ascribe steric interactions of the vinyl group to favor conformer **69** over **68**, which results in formation of the undesired *trans*-1-H/2-H configured product **70**.

While we had demonstrated the viability of a C−C bond construction from the amine-appended vinyl bromide in **67**, we recognized that prior formation of the B ring would be required to overcome formation of the undesired *trans*-ring junction. Consequently, β-amino ester **65** was sequentially α-allylated and subjected to ring-closing metathesis to furnish cyclopentene **71** (Scheme 10). As anticipated, the intramolecular Heck coupling proceeding via **72** now furnished bicyclic substructure **73** possessing the desired *cis*-1-H/2-H configuration. To access a saturated bicycle such as **74** from **73**, we investigated the diastereoselective hydrogenation, removal of the chiral auxiliary and installation of the α-quaternary center in the subsequent synthetic steps. Disappointingly, none of these transformations, executed in various orders, proved satisfactory. Removal of the methylbenzyl group proved unexpectedly challenging and could not be carried out with dissolving metal reductions, which led to complex product mixtures or decomposition. Alternatively, forcing, heterogeneous hydrogenations gave low yields of the corresponding saturated secondary amine, albeit as an inseparable diastereomeric mixture at C18 (~1:1 d.r.). Prior

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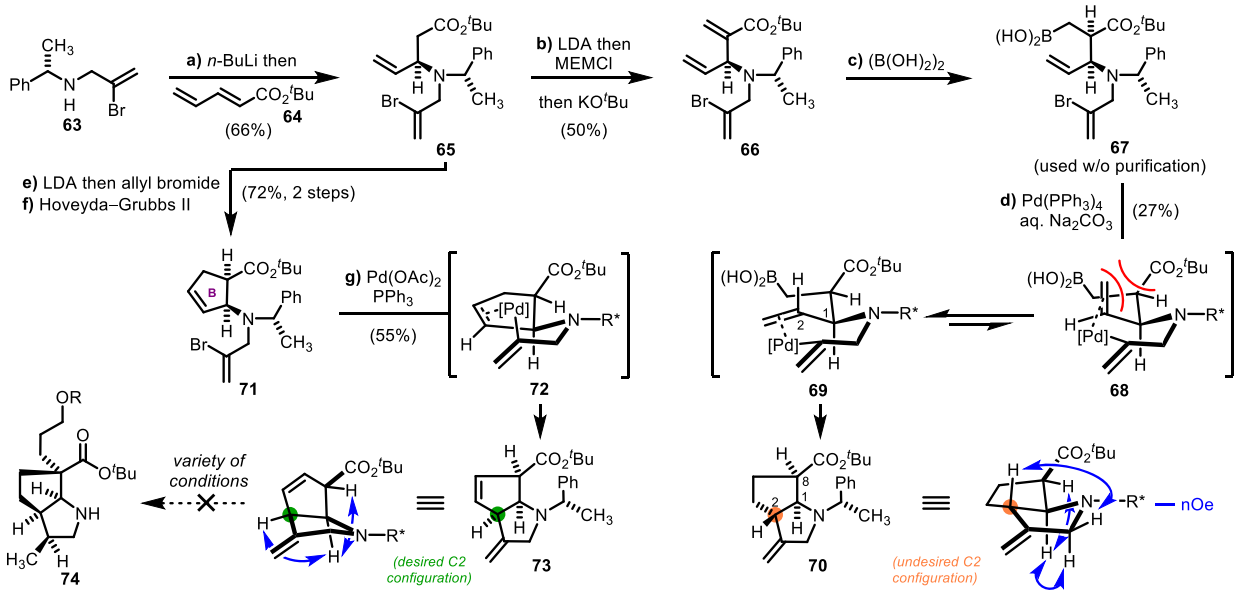
Scheme 10. Synthesis of *trans*-Bicycle 70 and *cis*-Bicycle 73[a]



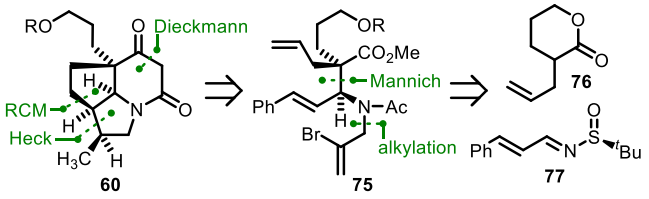
[a]Reagents and conditions: (a) *n*-BuLi, THF, −78 °C then **64** (66%); (b) LDA, THF, −78 °C then MEMCl, 0 °C then KO^{t}Bu, 23 °C (50%); (c) (B(OH$_2$)$_2$, CuCl, (2-biphenyl)dicyclohexylphosphine, NaO^{t}Bu, EtOH, 23 °C; (d) Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, THF, H$_2$O, 70 °C (27% **70**, 3% **C8-*epi*-70**); (e) LDA, THF, −78 °C then allyl bromide, 0 °C; (f) Hoveyda−Grubbs 2nd gen catalyst, CH$_2$Cl$_2$, 40 °C (72%, 2 steps); (g) Pd(OAc)$_2$, PPh$_3$, NEt$_3$, MeCN, 80 °C (55%). LDA = lithium diisopropylamide, MEMCl = 2-methoxyethoxymethyl chloride, Ac = CH$_3$CO.

saturation of the bicyclic structure via potentially more selective, homogeneous hydrogenation methods failed, presumably because of the presence of the basic tertiary amine. Furthermore, following numerous attempts to alkylate **73** (and derivatives thereof) using a variety of bases and electrophiles, installation of the α-quaternary center also remained unsuccessful.

Although having failed to further elaborate bicycle **73**, the auspicious bond constructions to build the bicycle that comprises the western portion of the calyciphylline B-type alkaloids had provided a lot of insight for revising the synthetic plan. Notably, we became cognizant of the importance of embedding the nitrogen as an amide, rather than amine, to enable an efficient diastereoselective hydrogenation. Furthermore, we were also encouraged to introduce the quaternary center earlier in the synthesis, thus circumventing a late-stage and challenging alkylation.

Mannich Approach.[20] At this stage, we envisioned a revised synthetic strategy to access tricycle **60** involving similar cyclization events as in the previous strategy (Scheme 11). However, as a major difference, acyclic β-amino ester **75** would incorporate the C8 quaternary center. While **75** contains the obvious retron for a Mannich reaction, literature precedent for the intermolecular enantio- and diastereoselective preparation of α,α-dialkylsubstituted Mannich products is scarce—particularly when the two α-substituents in the acyclic pronucleophile are nonequivalent.[51] The pertinent reported examples generally involve use of activated glyoxylate-derived imines,[52] hence making those methods less favorable for our goal to access **75** in a concise manner. Inspired by Ellman's pioneering work,[53] we eventually decided to construct β-amino ester **75** from allylated valerolactone **76**[54] and *N*-*tert*-butanesulfinyl imine **77**.[55] Cursory examination of the parameters for this transformation had shown that the γ-substituent in the imine would be required to avoid undesired 1,4-addition of the enolate.[29] While we faced some uncertainty regarding the diastereoselectivity at the α-quaternary center in this Mannich reaction, we reasoned that the choice of these particular substrates would be ideal in terms of accessing a suitably functionalized and oxidized product for rapid conversion to **75**. Moreover, the very high degree of molecular complexity generated in this Mannich reaction, namely, the construction of a key C−C bond with both the α-quaternary- and β-amino centers, would outweigh a potentially imperfect diastereoselectivity at the quaternary center.

Scheme 11. Revised Retrosynthetic Analysis of Tricycle 60



In practice and as expected, addition of the lithium enolate derived from **76** to sulfinyl imine **77** gave rise to a mixture of the epimeric Mannich products *SS*-**80** and *SR*-**80** (Scheme 12). However, the distribution of these β-amino lactone products was strongly influenced by the reaction temperature and time. Following optimization studies, we realized that this transformation encompassed a Mannich−retro-Mannich equilibration of the product β-amino lactones, where *SS*-**80** appeared to be the kinetic product that was obtained nearly exclusively following a short reaction time.[27] According to a Zimmerman−Traxler-type six-membered transition-state model,[53] we rationalized that *SS*-**80** and *SR*-**80** were formed via **78** and **79**, where either the allyl or lactone methylene group adopt a pseudo-axial disposition, respectively. Given the similar steric influence exerted by these two groups, we expected that under thermodynamic reaction conditions, a virtually equal distribution of the β-amino lactone products would be obtained.

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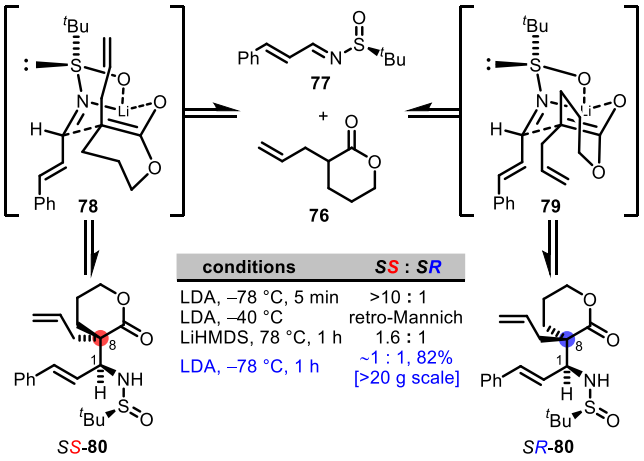
Scheme 12. Optimization of the Mannich Reaction[a]



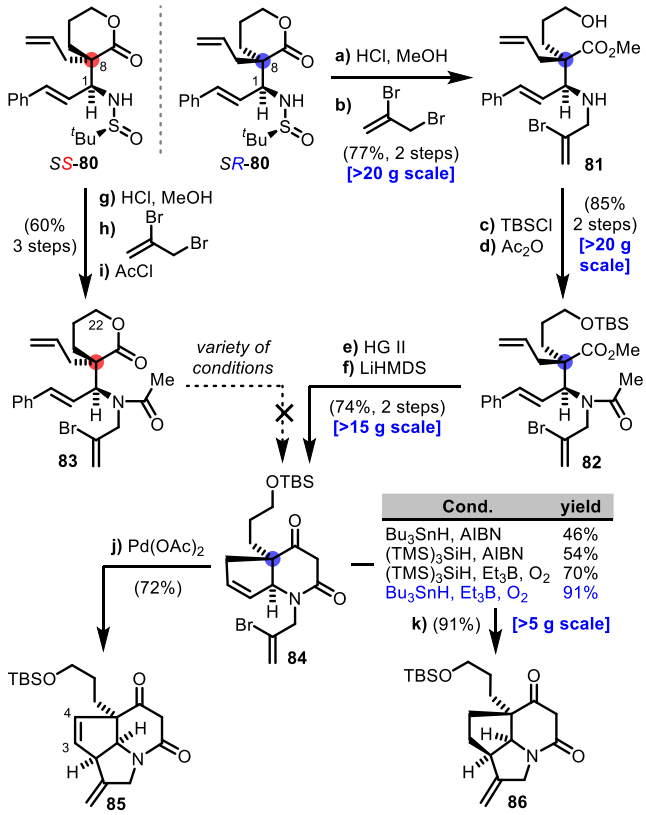
[a]Reagents and conditions: LDA, **76**, THF, −78 °C, then **77** (44%, 53% brsm *SS*-**80**; 38%, 45% brsm *RS*-**80**).

Indeed, following further experimentation, *β*-amino lactones *SS*-**80** and *SR*-**80** were ultimately formed as a ∼1:1 mixture in 82% combined yield on multigram scale.

Turning to the tricyclic core construction, we intended to utilize both *β*-amino lactones *SS*-**80** and *SR*-**80** in the forward synthesis (Scheme 13). With respect to use of *SS*-**80**, a formal inversion of the C8 stereocenter was envisioned that would then enable us to intercept the *SR*-synthetic route. First, the sulfinyl group in *SR*-**80** was removed with concomitant lactone methanolysis to give, after *N*-alkylation of the intermediate hydrochloride salt, vinyl bromide **81**. Following silylation and acetylation, amide **82** underwent sequential ring-closing metathesis and Dieckmann condensation to give decagram quantities of vinyl bromide-bearing bicycle **84**. Starting from *β*-amino lactone *SS*-**80**, a related synthetic sequence furnished amide **83**, whereupon a variety of attempts were made to formally invert the C8 stereocenter via anti-Markovnikov hydration of the allyl group and elimination of the C22 hydroxy group. In practice, numerous variants of hydroboration−oxidation, Wacker-type oxidation, oxidative cleavage−homologation, or silylation followed by Fleming−Tamao oxidation that were investigated proved unsuccessful in achieving the desired functionalization of the terminal olefin.[29] We suspect that the underlying, very densely and diversely functionalized, nature of amide **83** led to the many failed oxidation attempts, and we were unable to pinpoint any exact factors for this circumstance. Consequently, our plan to use *SS*-**80** in the synthetic route was abandoned, but the material could be recycled via retro-Mannich reaction to furnish imine **77** and allylated lactone **76**.[29] Returning to vinyl bromide bearing bicycle **84**, an intramolecular Heck coupling completed construction of the tricyclic substructure and furnished diene **85** in 72% yield. Alternatively, the tricyclic framework of **86** featuring a saturated B-ring could be accessed by means of a reductive radical cyclization. It was discovered that radical initiation with BEt_3/O_2 and use of Bu_3SnH as the reductant provided dehydro tricycle **86** in the highest yield on multigram scale.[27] Notably, a similar radical ring closure had not been successful in related substrates containing a tertiary amine instead of an amide (cf. **66** and **71**, Scheme 10).

With the tricyclic framework in place, our focus transitioned to completion of the challenging all-*cis* 1-H/2-H/18-H

Scheme 13. Synthesis of the Tricyclic Core[a]



[a]Reagents and conditions: (a) 4 M HCl in 1,4-dioxane, MeOH, 50 °C; (b) 2,3-dibromopropene, $^iPr_2NEt$, CH_3CN, 80 °C, (77%, 2 steps, +11% from 2nd cycle); (c) TBSCl, imidazole, CH_2Cl_2, 0 to 23 °C (89%); (d) Ac_2O, PhH, 90 °C (96%); (e) Hoveyda−Grubbs 2nd gen catalyst (HG II), CH_2Cl_2, 40 °C (82%); (f) LiHMDS, THF, −78 °C (90%); (g) 4 M HCl in 1,4-dioxane, MeOH, 0 to 23 °C; (h) 2,3-dibromopropene, $^iPr_2NEt$, CH_3CN, 80 °C, (54%, 2 steps, +17% from 2nd cycle); (i) AcCl, $^iPr_2NEt$, DMAP, CH_2Cl_2, 23 °C (85%); (j) $Pd(OAc)_2$, PPh_3, NEt_3, MeCN, 50 °C (72%); (k) Bu_3SnH, Et_3B, O_2, PhH, 23 °C (91%). DMAP = *N*,*N*-dimethylaminopyridine, AIBN = azobisisobutyronitrile.

substructure (Scheme 14). While heterogeneous hydrogenations of diene **85** gave rise to complex mixtures of products, a two-step protocol using Crabtree's catalyst for reduction of the 1,1′-disubstituted alkene, followed by Pd/C-catalyzed hydrogenation of ΔC3−C4, ultimately afforded tricycle **87**, albeit as a 4:1 mixture of diastereomers over a reaction time that exceeded 1 week. Fortunately, dehydro tricycle **86** emerged as a far more favorable substrate for the diastereoselective hydrogenation, especially because its saturated B-ring created a sterically more biased concave face. In this respect, reaction optimizations revealed the use of the $Pd(OH)_2$ catalyst at reduced hydrogen pressure to be ideal, which gave access to tricycle **87** in excellent diastereoselectivity.[27] A survey of various solvents identified dichloromethane to be unique in enabling rapid initial isomerization of the *exo*-olefin to enamide **88**, prior to hydrogenation. The optimized route to **87**, proceeding in nine overall steps, provided multigram scale access to the tricyclic substructure containing four contiguous stereocenters.

Next, the diastereoselective installation of the C5−C7 substituents in the piperidinedione substructure was investigated (Scheme 15a). Alkylation of the 1,3-dicarbonyl system

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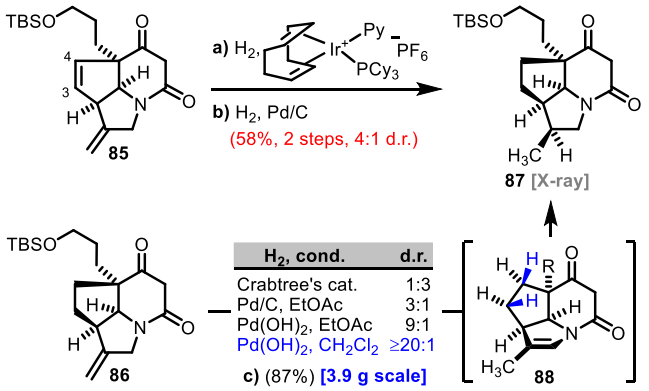
Scheme 14. Diastereoselective Hydrogenation of the Tricyclic Framework[a]



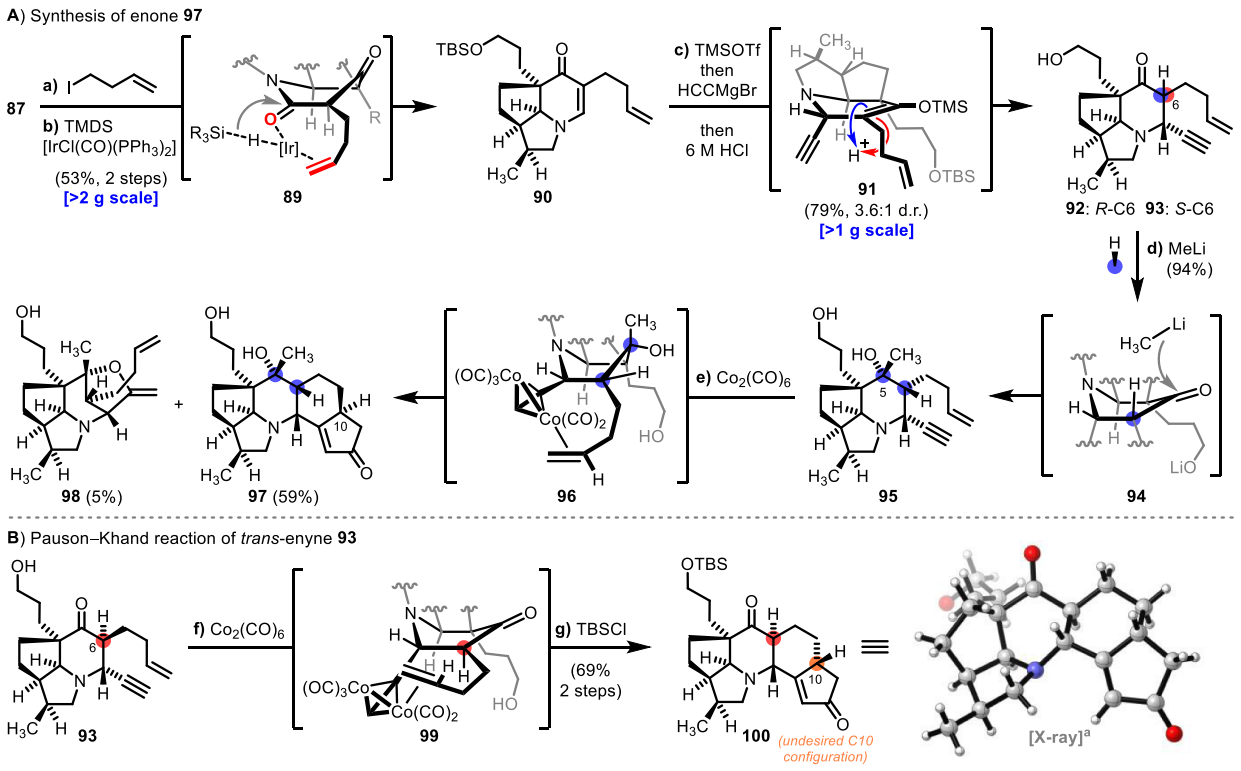
[a]Reagents and conditions: (a) 50 atm H_2, [Ir(cod) (PCy_3) (py)]PF_6, CH_2Cl_2, 23 °C; (b) 1 atm H_2, Pd/C, $NaHCO_3$, MeOH, 23 °C (58%, 2 steps, 4:1 d.r.); (c) 1 atm H_2/Ar (1:1), $Pd(OH)_2$, CH_2Cl_2, 23 °C, (87%, ≥20:1 d.r.).

in **87** was complicated by formation of di-, C-, and O-alkylated product mixtures using a wide variety of base (K_2CO_3, Cs_2CO_3, LiHMDS, NaH, NaO^{t}Bu, and KO^{t}Bu) and solvent [THF, acetone, PhMe, *N*,*N*-dimethylformamide (DMF), DMSO, ^{t}BuOH, MeCN, and NMP] combinations. Eventually, we identified homoallyl iodide to exhibit a marked improvement in terms of C-selectivity in DMF solvent, compared to the corresponding bromide, and the resulting product was obtained in 62% yield. For the ensuing conversion to enaminone **90**, we initially explored transient protection of the ketone as the enolate or silyl enol ether, followed by treatment with various metal hydrides to reduce the δ-lactam. However, hydride additions to this electron-rich system proved unsuccessful and led us instead to seek a direct, amide-selective reduction of the 1,3-dicarbonyl system. Following a survey of a wide range of existing methods,[56] only Dixon's reported combination of Vaska's complex and TMDS was successful in selectively reducing the lactam amide in the presence of both the ketone and very sensitive terminal olefin groups.[8,57]

Surprisingly, the analogous reduction prior to introduction of the homoallyl group (i.e., reduction of tricycle **87**) was unsuccessful, suggesting that the terminal olefin might act as an auxiliary directing group in this remarkably chemoselective transformation (see **89**).

Addition of ethynylmagnesium bromide to the triflate salt derived from enaminone **90** took place from the sterically less encumbered α-face and furnished the intermediate silyl enol ether, **91**, as a single diastereomer. While exposure of the latter compound to TBAF furnished C6-epimeric enynes **92** and **93** in a ~1:2 ratio, acid hydrolysis afforded *cis*-enyne **92** as the major product (3.6:1 d.r.). This stereochemical outcome can be rationalized by the (kinetically) favored protonation occurring from the more accessible face that is *cis* to 7-Hβ. Methyl addition to the carbonyl group in **92** then occurred exclusively from the β-face (**94**), by virtue of the preferred

Scheme 15. Elaboration of Tricyclic Core 87 and Construction of the Full Calyciphylline B-type Carbon Framework[a]



[a]Reagents and conditions: (a) NaH, 4-iodo-butene, DMF, 0 °C (62%, 72% brsm); (b) TMDS, [IrCl(CO) (PPh_3)$_2$], PhMe, 23 °C (73%, +13% from 2nd cycle); (c) TMSOTf, CH_2Cl_2, −78 °C, then HCCMgBr, THF, −78 to 0 °C, then aq 6 M HCl, 0 to 23 °C (62% **92**; 17% **93**); (d) **92**, $LaCl_3$·2LiCl, THF, 23 °C, then MeLi, −25 °C (94%, ≥20:1 d.r.); (e) $Co_2(CO)_8$, CH_2Cl_2, 23 °C, then MeCN, TMANO·$2H_2O$, −78 to 23 °C (59% **97**; 5% **98**); (f) $Co_2(CO)_8$, CH_2Cl_2, 23 °C, then TMANO·$2H_2O$, 0 to 23 °C; (g) TBSCl, imidazole, CH_2Cl_2, 23 °C (69%, 2 steps). TMDS = 1,1,3,3-tetramethyldisiloxane, TMS = trimethylsilyl, TMANO = trimethylamine *N*-oxide. [b]TBS omitted for clarity.

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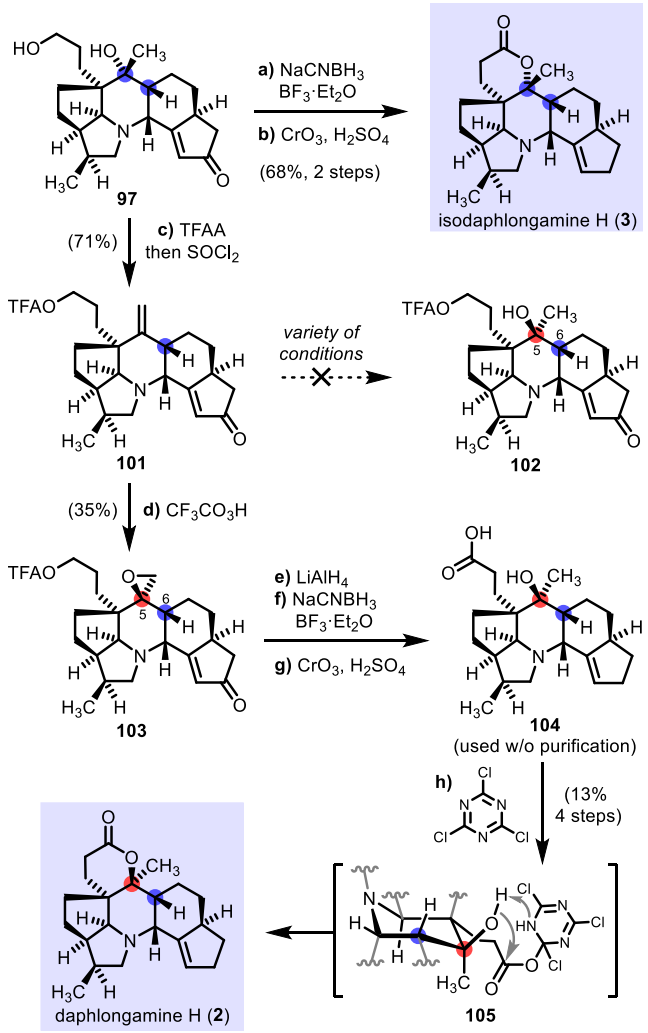
nucleophile trajectory being *cis* to 6-Hβ. Notably, the lanthanum(III) chloride bis(lithium chloride) complex was identified as an essential additive to achieve appreciable conversion in this transformation.[58] Enyne diol **95** underwent amine-*N*-oxide-promoted Pauson–Khand reaction[59] to furnish pentacyclic enone **97** together with trace amounts of enol ether **98**, as a consequence of competing hydroalkoxylation of the alkyne moiety. The *cis*-enyne disposition had resulted in a corresponding insertion of the cobalt complex to the appended olefin group (**96**) to install 10-Hα in the desired orientation. It was corroborated that the C5 tertiary hydroxy group does not influence the generated C10 stereocenter, as Pauson–Khand reaction of *cis*-enyne **92** (prior to methyllithium addition) gave rise to the same 10-Hα orientation. Having also gained access to *trans*-enyne **93**, featuring the *S*-C6 configuration that is present in deoxycalyciphylline B (**1**), analogous construction of the E and F rings was investigated (Scheme 15b). Unfortunately, subjecting **93** to sequential Pauson–Khand reaction (**99**) and silylation of the primary hydroxy group gave enone **100** whose undesired C10 stereochemistry was confirmed by single-crystal X-ray analysis. We were unable to alter this stereochemical outcome, and attempts to epimerize 10-Hβ in enone **100** via γ-deprotonation or siloxydiene formation were met with failure, leading us not to pursue a synthesis of deoxycalyciphylline B (**1**).

With the full carbon framework of the calyciphylline B-type natural products in place, we discovered that treatment of enone **97** with excess sodium cyanoborohydride in the presence of boron trifluoride diethyl etherate[60] cleanly furnished the corresponding cyclopentene (Scheme 16). This highly efficient one-step deoxygenation protocol proved far superior to other methods that were investigated (such as Wolff–Kishner-, Clemmensen-type reductions, dithiane formation/Raney Ni, or $LiAlH_4/AlCl_3$).[61] The *cis*-lactone was finally installed via Jones oxidation and completed the total synthesis of isodaphlongamine H (**3**), which displayed analytical data in excellent agreement with Hanessian's report.[19]

For the synthesis of daphlongamine H (**2**), we were challenged to invert the tertiary alcohol in **97**. The strong steric bias in the precursor carbonyl derivative (i.e., enyne **92**) had prevented us from accessing the opposite configuration at C5 by addition of different methyl nucleophiles. Consequently, we pursued a formal dehydration–rehydration sequence on enone **97** which was initiated with the synthesis of alkene **101**. Subjecting the exocyclic alkene to Mn- and Co-catalyzed radical hydrofunctionalizations[62] returned either unreacted starting material or led to nonspecific decomposition, and **102** could not be accessed. Various other conventional methods (such as oxymercuration, *m*-CPBA epoxidations, dihydroxylation, or halohydrin formation) were equally unsuccessful in oxygenating the exomethylene in **101**. Ultimately, trifluoroperacetic acid enabled oxidation of the sterically hindered alkene in the presence of the proximal tertiary amine[63] and furnished epoxide **103**, albeit in 35% yield. Next, epoxide **103** was reduced with lithium aluminum hydride to give an intermediate triol that was subjected to the established deoxygenation conditions. After oxidation of the resulting amino diol, the lactonization of the resulting highly polar *trans*-seco acid **104** proved unexpectedly challenging. We noted that for formation of the highly strained *trans*-lactone in **2**, in comparison to the facile *cis*-lactonization in isodaphlongamine H (**3**), the central piperidine ring would need to undergo a

Scheme 16. Synthesis of Isodaphlongamine H (3) and Daphlongamine H (2)[a]



[a]Reagents and conditions: (a) $NaCNBH_3$, $BF_3{\cdot}Et_2O$, THF, 23 to 66 °C; (b) CrO_3, H_2SO_4, H_2O, acetone, 0 °C (68%, 2 steps); (c) TFAA, CH_2Cl_2, −78 °C, then $SOCl_2$, −78 to 0 °C (71%); (d) aq. H_2O_2, TFAA, CH_2Cl_2, 0 to 23 °C (35%); (e) $LiAlH_4$, THF, −78 to 66 °C; (f) $NaCNBH_3$, $BF_3{\cdot}Et_2O$, THF, 23 to 66 °C; (g) CrO_3, H_2SO_4, H_2O, acetone, 0 °C; (h) cyanuric chloride, NEt_3, MeCN, 23 °C (13%, 4 steps).

drastic conformational change to place the C5-hydroxy group in a pseudo-equatorial orientation. While mildly acidic conditions or simple thermal activation of **104** did not afford any desired lactone product, we discovered that cyanuric chloride was a suitable promoter of the final bond formation.[64] This successful *trans*-lactone formation is probably driven by a double activation of the carboxy and hydroxy groups (**105**) and completed the total synthesis of daphlongamine H (**2**). Our synthetic route gave rise to daphlongamine H (**2**) in 20 steps from imine **77** (longest linear sequence) and constitutes the first total synthesis of this calyciphylline B-type alkaloid.

Structural Revision. By virtue of our synthetic route, which provided sufficient amounts of materials for follow-up characterization studies, and following interpretation of 2D NMR data (900 MHz spectrometer) of synthetic daphlongamine H (**2**), we were confident in our assignment of the *R*-C6 stereochemistry. However, we were initially surprised to find

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that our NMR spectra were in good agreement with those reported for (*S*-C6 configured) deoxyisocalyciphylline B (Figure 2a).[14] Eventually, careful analysis of the reported 2D

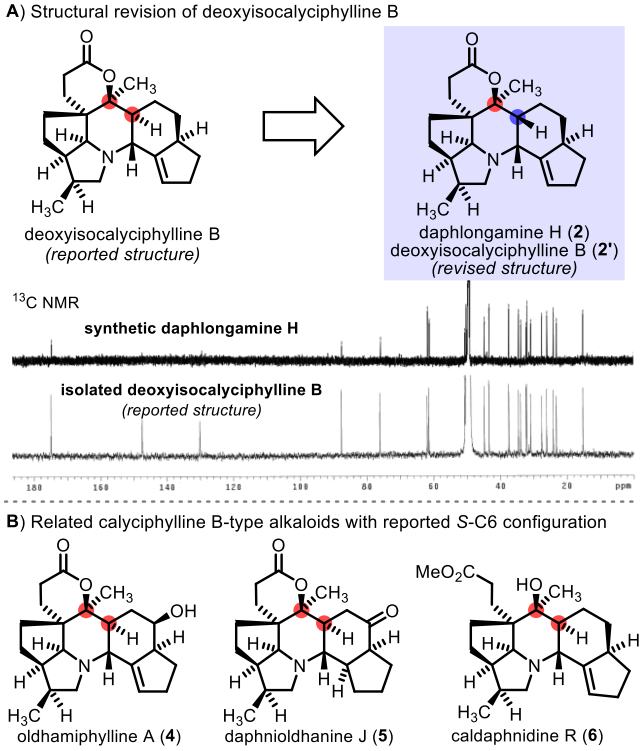

Figure 2. (A) $^{13}C\{^1H\}$ NMR spectra comparison of synthetic daphlongamine H (**2**) and deoxyisocalyciphylline B (reported structure). (B) Related calyciphylline B-type alkaloids with reported *S*-C6 configuration that were structurally assigned by analogy to (misassigned) deoxyisocalyciphylline B.

NOESY spectrum of deoxyisocalyciphylline B revealed that the *S*-C6 stereochemistry had been misassigned,[29] and we established that isolated deoxyisocalyciphylline B (revised structure: **2′**) and daphlongamine H (**2**) are the same natural product. Furthermore, we concluded that the spectroscopic data reported for daphlongamine H (**2**) corresponds to its likely ammonium salt. Thus, NMR experiments of our synthetic daphlongamine H (**2**) using old $CDCl_3$ (putatively containing residual acid) led to spectra which were in agreement with the values reported for naturally occurring **2**.

Our structural revision of deoxyisocalyciphylline B raises concern regarding the reported structures of the related calyciphylline B-type alkaloids oldhamiphylline A (**4**),[16a] daphnioldhanine J (**5**),[16b] and caldaphnidine R (**6**)[17b] that were reported to also feature an *S*-C6 configuration (Figure 2b). The structures of these latter three natural products were to some extent established by analogy to (previously reported and misassigned) deoxyisocalyciphylline B, and thus a similar revision of the C6 stereochemistry might be required for these cases as well.

The pertinent NMR spectra (NOESY) enabling us to verify the C6 configurations of oldhamiphylline A (**4**), daphnioldhanine J (**5**), and caldaphnidine R (**6**) were not included in the isolation papers.[16,17] However, comparison of the $^{13}C\{^1H\}$ NMR shifts of C6 reported for **4** (δ_{CD_3OD}: 44.6 ppm) and **5** (δ_{CDCl_3}: 42.6 ppm) with *S*-C6 configured deoxycalyciphylline B (**1**) (δ_{CDCl_3}: 47.8 ppm) and *R*-C6 configured daphlongamine H (**2**) (δ_{CDCl_3}: 40.8 ppm; δ_{CD_3OD}: 42.9 ppm) indicates that the reported values are more in line with an *R*-C6 configuration, suggesting that **4** and **5** likely have been misassigned. Because the methanolysis product **6** was structurally elucidated by NMR data comparison with (previously isolated and misassigned) deoxyisocalyciphylline B, its C6 configuration in all probability also was misassigned. At this stage, the suspected occurrence of the calyciphylline B-type alkaloids as a diastereomeric C5/C6 quartet that result biosynthetically from a nonselective hydroacyloxylation remains highly speculative.[14,18] Because only the natural existence of deoxycalyciphylline B (**1**) and daphlongamine H (**2**) is unambiguously confirmed to date (by X-ray analysis and total synthesis, respectively), it may rather be that the appended propionic acid side chain undergoes hydroacyloxylation onto the tetrasubstituted olefin from either the α- or β-face via intramolecular proton transfer (Figure S11),[29] thus only resulting in calyciphylline B-type alkaloids with corresponding C5/C6 configurations as found in **1** and **2**.

CONCLUSIONS

We have reported the evolution of strategies toward the total synthesis of calyciphylline B-type natural products, a subfamily of the polycyclic *Daphniphyllum* alkaloids. Our initial efforts to construct the central piperidine ring via 6π-azaelectrocyclization revealed a wealth of interesting reactivity surrounding oxazaborinine heterocycles, which were ultimately unsuccessful as intermediates in the total synthesis effort. A different strategy encompassing an intramolecular Heck−Suzuki coupling cascade and diastereoselective hydrogenation highlighted synthetic challenges in forming the western all-*cis* methine substructure of the calyciphylline B-type alkaloids and eventually inspired a successful approach. Therein, a key complexity-building Mannich reaction was developed in the opening step. Elaboration of the resulting β-amino lactone gave access to a highly functionalized acyclic precursor which underwent carefully orchestrated and efficient cyclizations to forge the fused, hexacyclic framework of the natural products in a diastereoselective manner. Our synthetic studies culminated in the first total synthesis of daphlongamine H (**2**), gave access to isodaphlongamine H (**3**), and also led to revision of the reported structure of deoxyisocalyciphylline B.

EXPERIMENTAL SECTION

General information: Unless otherwise noted, all reactions were performed in flame or oven-dried glassware fitted with rubber septa under a positive pressure of nitrogen using standard Schlenk techniques. Air- and moisture-sensitive liquids were transferred via a syringe or stainless steel cannula through rubber septa. Solids were added under inert gas or were dissolved in appropriate solvents and added using a needle and syringe. Low-temperature reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (−78 °C), H_2O/ice (0 °C). Reaction temperatures above 23 °C were conducted in an oil bath or in a heated metal block (reactions conducted in vials). The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC) using glass plates precoated with silica gel (Silicycle Siliaplates, glass backed, extra hard layer, 60 Å, 250 μm thickness, F254 indicator). TLC plates were visualized by exposure to ultraviolet light (254 nm), were stained by submersion in aqueous potassium permanganate solution ($KMnO_4$) or ceric ammonium molybdate solution, and were developed by heating with a heat gun. Flash-column chromatography on silica gel was performed as described by

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Still et al.,[65] employing silica gel (Silicycle silica gel, 40−63 μm particle size). Organic solutions were concentrated under reduced pressure on a Heidolph temperature-controlled rotary evaporator equipped with a dry ice/isopropanol condenser. All yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C{^{1}H} NMR) pure material. Materials: Unless noted below, commercial reagents were purchased from MilliporeSigma, Acros Organics, Chem-Impex, Oakwood Chemical, Combi-blocks, TCI, and/or Alfa Aesar and used without additional purification. Solvents were purchased from Fisher Scientific, Acros Organics, Alfa Aesar, and Sigma-Aldrich. THF, diethyl ether (Et_2O), acetonitrile (MeCN), benzene (PhH), toluene (PhMe), methanol (MeOH), and triethylamine (Et_3N) were sparged with argon and dried by passing through alumina columns using argon in a Glass Contour solvent purification system. Dichloromethane (CH_2Cl_2, DCM) and diisopropylamine (DIPA) were freshly distilled over calcium hydride under a N_2 atmosphere prior to use. NMR spectroscopy: NMR spectral data were obtained using deuterated solvents, obtained from Cambridge Isotope Laboratories, Inc. ^{1}H NMR and ^{13}C{^{1}H} NMR data were recorded on Bruker spectrometers operating at 400, 500, 600, 700, or 900 MHz for proton nuclei (and 100, 125, 150, 175, or 225 MHz for carbon nuclei). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, C_6HD_5: δ 7.16, CHD_2OD: δ 3.31). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, C_6D_6: δ 128.06, CD_3OD: δ 47.67). ^{19}F NMR spectra were acquired on a Bruker AVQ-400 spectrometer and internally referenced to $CFCl_3$ (δ 0.00). ^{11}B NMR spectra were acquired on an AVB-400 or AV-600 spectrometer, and chemical shifts were referenced to an external reference $BF_3{\cdot}OEt_2$ (δ 0.00). When ^{13}C signals appeared too weak and/or broad, HMBC and HSQC spectra were acquired to confirm signal authenticity. ^{1}H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants J (Hz), integration) (e.g., "5.21 (t, ^3J = 7.3 Hz, 1H)"). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), se (sextet), h (heptet), m (multiplet), and app (apparent multiplicity). In the case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported as the center of the resonance range. Data for ^{13}C, ^{19}F, and ^{11}B NMR spectroscopy are reported in terms of chemical shift (δ ppm). In addition to 1D NMR experiments, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond coherence (HMBC), and nuclear Overhauser enhancement spectroscopy (NOESY) were used to assist structure elucidation. All raw FID files were processed, and the spectra were analyzed using the program MestReNOVA 11.0 from Mestrelab Research S. L. The AVB-400, AVQ-400, AV-500, DRX-500, and AV-600 instruments were partially supported by NIH grants SRR023679A, RR02424A-01, S10RR03353-01, and 1S10RR016634-01, and NSF grants CHE-9633007, CHE-8208992, CHE-0130862, and CHE-8703048. The AV-700 instrument was supported by the Berkeley College of Chemistry NMR facility. Funds for the QB3 900 MHz NMR spectrometer were provided by the NIH through grant GM68933. Mass spectrometry: High-resolution mass spectra (HRMS) were obtained from the Mass Spectral Facility at the University of California, Berkeley, on a PerkinElmer AxION 2 UHPLC-TOF Instrument (ESI) or a Waters AutoSpec Premier mass spectrometer (EI). Data acquisition and processing were performed using the XcaliburTM software. IR spectroscopy: IR spectroscopic data were recorded on a Bruker ALPHA FT-IR spectrophotometer using a diamond attenuated total reflectance (ATR) accessory. If required, substances were dissolved in dichloromethane prior to direct application on the ATR unit. Data are represented as follows: frequency of absorption (cm^{-1}) and intensity of absorption (s = strong, m = medium, w = weak, br = broad). HPLC analyses. Analytical HPLC on the chiral stationary phase was performed on a computer-operated PerkinElmer system (Flexar HPLC system). Column, oven temperature, solvent system, flow rate, detection mode, and retention times are given in the relevant section of the experimental part. Optical rotations: Optical rotations were acquired on a PerkinElmer 241 Polarimeter. Melting points: Melting points were measured on a Laboratory Devices Mel-Temp II.

Experimental Details. Compounds **2**, **3**, **41**−**43**, and **80**−**103** (synthetic procedures, characterization data, NMR spectra, and X-ray structures), as well as the natural product NMR spectra comparison, and discussion of the structural revision have been previously reported by us[20,34] and are not reproduced here.

*Synthesis of (4R,5S)-5-Methyl-4-((triisopropylsilyl)ethynyl)-tetrahydro-2H-pyran-2-one (**25**).* According to Hayashi's method,[24] a flask was charged with propargyl alcohol **24** (6.33 g, 17.4 mmol, 1.1 equiv), $[RhCl(cod)]_2$ (194 mg, 0.40 mmol, 2.5 mol %), and Cs_2CO_3 (515 mg, 1.58 mmol, 0.1 equiv). A solution of known α,β-unsaturated lactone **23**[23] (1.77 g, 15.8 mmol, 1.0 equiv) in N_2-sparged (1 h) toluene (45 mL) was then added, and the resulting orange mixture was heated to 80 °C. After 36 h, the mixture was cooled to 23 °C and filtered through a pad of Celite, eluting with ethyl acetate (200 mL). The filtrate was concentrated, and the crude residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to give lactone **25** (2.36 g, 8.02 mmol, 51%) as a yellow oil. TLC (20% ethyl acetate in hexanes): R_f = 0.33 ($KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.38 (dd, J = 11.5, 4.4 Hz, 1H), 3.92−3.86 (m, 1H), 2.99−2.90 (m, 1H), 2.64−2.54 (m, 2H), 2.09−2.00 (m, 1H), 1.14 (d, J = 6.7 Hz, 3H), 1.10−1.00 (m, 21H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 169.1, 107.3, 84.1, 73.7, 35.8, 34.1, 32.5, 18.6, 14.9, 11.1. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2941 (m), 2863 (s), 1737 (s), 1215 (s), 1048 (s), 882 (s), 675 (s). HRMS (ESI): calcd for ($[M + Na]$ $C_{17}H_{30}NaO_2Si)^+$, 317.1907; found, 317.1907. $[\alpha]_D^{20}$ = −25.0° (c = 2.2, CH_2Cl_2).

*Synthesis of (2S,3R)-3-(2-(Methoxy(methyl)amino)-2-oxoethyl)-2-methyl-5-(triisopropylsilyl)pent-4-yn-1-yl methanesulfonate (**26**).* A solution of lactone **25** (960 mg, 3.26 mmol, 1.0 equiv) in THF (20 mL) was treated sequentially with *N*,*O*-dimethylhydroxylamine hydrochloride (477 mg, 4.89 mmol, 1.5 equiv) and isopropylmagnesium chloride solution (2 M in THF, 4.89 mL, 9.78 mmol, 3.0 equiv) at 0 °C. After 20 min, the mixture was diluted with saturated aqueous ammonium chloride solution (50 mL) and dichloromethane (50 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 × 40 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The residue was used in the next step without further purification. A solution of the crude alcohol (assuming 3.26 mmol) in dichloromethane (20 mL) was treated sequentially with triethylamine (1.36 mL, 9.78 mmol, 3.0 equiv) and methanesulfonyl chloride (378 μL, 4.89 mmol, 1.5 equiv) at 0 °C. After 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (20 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (40% → 50% ethyl acetate in hexanes) to give Weinreb amide **26** (1.08 g, 2.49 mmol, 76% over 2 steps) as a white solid. TLC (50% ethyl acetate in hexanes): R_f = 0.32 ($KMnO_4$).^{1}H NMR (700 MHz, $CDCl_3$): δ 4.22−4.13 (m, 2H), 3.69 (s, 3H), 3.36−3.30 (m, 1H), 3.17 (s, 3H), 3.13 (s, 1H), 3.02 (s, 3H), 2.79 (dd, J = 15.8, 7.6 Hz, 1H), 2.51 (dd, J = 15.8, 7.1 Hz, 1H), 2.14−2.06 (m, 1H), 1.08−0.97 (m, 24H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 171.5, 106.8, 84.4, 72.9, 61.5, 37.5, 35.4, 35.1 (br), 32.3 (br), 31.7, 30.2, 18.7, 11.6, 11.3. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2940 (m), 2864 (m), 1659 (s), 1462 (m), 1355 (s), 1174 (s), 961 (s), 883 (s), 835 (s), 677 (s). HRMS (ESI): calcd for ($[M + H]$ $C_{20}H_{40}NO_5SSi)^+$, 434.2391; found, 434.2399. $[\alpha]_D^{20}$ = −46.9° (c = 1.0, CH_2Cl_2). mp 40−45 °C.

*Synthesis of (2S,3R)-3-(2-Hydroxyethyl)-2-methyl-5-(triisopropylsilyl)pent-4-yn-1-yl Methanesulfonate (**27**).* A solution

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of Weinreb amide **26** (1.00 g, 2.31 mmol, 1.0 equiv) in THF (15 mL) was treated with lithium aluminium hydride (70.0 mg, 1.84 mmol, 0.8 equiv) at 0 °C. After 15 min, the mixture was diluted with diethyl ether (40 mL), water (280 μL), and aqueous sodium hydroxide solution (15 wt %, 70.0 μL). The mixture was warmed to 23 °C and stirred vigorously. After 15 min, magnesium sulfate was added and stirring was continued. After further 15 min, the mixture was filtered through a pad of Celite, eluting with diethyl ether (100 mL), and the filtrate was concentrated in vacuo. The residue was used in the next step without further purification. A solution of the crude aldehyde (assuming 2.31 mmol) in dichloromethane (15 mL) and methanol (3 mL) was treated with sodium borohydride (87.0 mg, 2.31 mmol, 1.0 equiv) at 0 °C. After 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (20 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (30% → 50% ethyl acetate in hexanes) to give alcohol **27** (773 mg, 2.05 mmol, 89% over 2 steps) as a white solid. TLC (50% ethyl acetate in hexanes): R_f = 0.22 ($KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.22−4.12 (m, 2H), 3.88−3.77 (m, 2H), 3.01 (s, 3H), 2.90 (dt, *J* = 10.7, 4.2 Hz, 1H), 2.05−1.98 (m, 1H), 1.84 (s, 1H), 1.82−1.75 (m, 1H), 1.69−1.61 (m, 1H), 1.09−0.97 (m, 24H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 107.3, 84.9, 73.0, 61.2, 37.3, 36.4, 35.8, 30.8, 18.74, 18.73, 11.6, 11.3. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3640 (br), 3379 (br), 2940 (s), 2864 (s), 1462 (m), 1354 (s), 1174 (s), 960 (s), 882 (m), 837 (m), 668 (s). HRMS (ESI): calcd for ([M + Na] $C_{18}H_{36}NaO_4SSi)^+$, 399.1996; found, 399.1971. $[\alpha]_D^{20}$ = −19.9° (*c* = 1.0, CH_2Cl_2). mp 50−55 °C.

*Synthesis of (2S,3R)-3-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-2-Methylpent-4-yn-1-yl Methanesulfonate (**28**).* A solution of alcohol **27** (690 mg, 1.83 mmol, 1.0 equiv) in THF (10 mL) was treated with tetrabutylammonium fluoride (TBAF) solution (1 M in THF, 3.67 mL, 3.67 mmol, 2.0 equiv) at 0 °C. After 1 h, the mixture was diluted with saturated aqueous sodium bicarbonate solution (20 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The residue was used in the next step without further purification. A solution of the crude alkyne (assuming 1.83 mmol) in dichloromethane (15 mL) was treated sequentially with imidazole (378 mg, 5.49 mmol, 3.0 equiv) and *tert*-butyldimethylsilyl chloride (414 mg, 2.75 mmol, 1.5 equiv) at 0 °C. After 20 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (10% → 20% ethyl acetate in hexanes) to give silyl ether **28** (605 mg, 1.81 mmol, 99% over 2 steps) as a colorless liquid. TLC (30% ethyl acetate in hexanes): R_f = 0.39 ($KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.18 (dd, *J* = 9.8, 8.3 Hz, 1H), 4.13 (dd, *J* = 9.7, 6.1 Hz, 1H), 3.78−3.70 (m, 2H), 3.00 (s, 3H), 2.87−2.83 (m, 1H), 2.07 (d, *J* = 2.5 Hz, 1H), 2.05−1.98 (m, 1H), 1.74−1.67 (m, 1H), 1.65−1.58 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 83.3, 72.8, 71.9, 60.7, 37.3, 35.9, 35.6, 29.1, 26.0, 18.4, 11.5, −5.2, −5.3. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3284 (w), 2929 (m), 2856 (m), 1471 (m), 1356 (s), 1175 (s), 1101 (s), 960 (s), 829 (s), 775 (s), 637 (m). HRMS (ESI): calcd for ([M + Na] $C_{15}H_{30}NaO_4SSi)^+$, 357.1526; found, 357.1540. $[\alpha]_D^{20}$ = +1.2° (*c* = 1.0, CH_2Cl_2).

*Synthesis of N-Allyl-N-((2S,3R)-3-(2-((tert-butyldimethylsilyl)-oxy)ethyl)-2-methylpent-4-yn-1-yl)-2,2,2-trifluoroacetamide (**29**).* A solution of silyl ether **28** (1.90 g, 5.69 mmol, 1.0 equiv) in acetonitrile (5.5 mL) was treated with triethylamine (950 μL, 6.82 mmol, 1.2 equiv), allylamine (6.40 mL, 85.3 mmol, 15 equiv), and sodium iodide (1.28 g, 8.53 mmol, 1.5 equiv) at 23 °C. The resulting mixture was heated to 45 °C. After 72 h, the mixture was cooled to 23 °C and then was filtered through a pad of Celite, eluting with ethyl acetate (100 mL). The filtrate was concentrated in vacuo, and the residue was used in the next step without further purification. A solution of the crude secondary amine (assuming 5.69 mmol) in dichloromethane (60 mL) was treated sequentially with triethylamine (2.37 mL, 17.1 mmol, 3.0 equiv) and trifluoroacetic anhydride (950 μL, 6.83 mmol, 1.2 equiv) at −78 °C. After 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (50 mL) and warmed to 23 °C. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (10% → 20% ethyl acetate in hexanes) to give amide **29** (1.76 g, 4.50 mmol, 79% over 2 steps) as a red oil. TLC (10% ethyl acetate in hexanes): R_f = 0.39 (UV/$KMnO_4$). *Note*: As determined by NMR spectroscopy, amide **29** exists as a mixture of rotamers (3:1 ratio) at 23 °C. In cases where the proton or carbon atoms show a double set of signals, the signal of the minor rotamer is marked with an asterisk. ^{1}H NMR (700 MHz, $CDCl_3$): δ 5.81−5.68 (m, 1H), 5.30−5.19 (m, 2H), 4.28* (dd, *J* = 15.1, 5.5 Hz, 1H), 4.16 (dd, *J* = 16.6, 4.8 Hz, 1H), 4.00 (dd, *J* = 16.6, 6.6 Hz, 1H), 3.87* (dd, *J* = 15.1, 6.7 Hz, 1H), 3.79−3.68 (m, 2H), 3.51 (dd, *J* = 13.4, 6.5 Hz, 1H), 3.36* (dd, *J* = 14.7, 6.6 Hz, 1H), 3.22 (dd, *J* = 13.6, 8.5 Hz, 1H), 2.71−2.62 (m, 1H), 2.16−2.08 (m, 2H), 2.00−1.93* (m, 1H), 1.75−1.65 (m, 1H), 1.63−1.55 (m, 1H), 0.97−0.91 (m, 3H), 0.91−0.84 (m, 9H), 0.06−0.03 (m, 6H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 157.4 (q, *J* = 35.5 Hz) 132.2, 131.2*, 119.2, 118.8*, 116.6 (q, *J* = 287.9 Hz), 84.1, 83.4*, 72.1*, 71.9, 60.7, 60.6*, 51.5, 51.3 (br), 49.6, 36.1*, 36.0, 35.1*, 34.1, 30.5*, 30.0, 26.0*, 26.0, 18.4*, 18.4, 12.9*, 12.3, −5.2, −5.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.05*, −68.16. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3310 (w), 2953 (m), 2929 (m), 2857 (m), 1690 (s), 1204 (s), 1170 (s), 1141 (s), 1098 (s), 830 (s), 811 (m), 775 (s). HRMS (ESI): calcd for ([M + Na] $C_{19}H_{32}F_3NNaO_2Si)^+$, 414.2047; found, 414.2048. $[\alpha]_D^{20}$ = −26.5° (*c* = 1.0, CH_2Cl_2).

*Synthesis of (R)-1,2,3,6,7,7a-Hexahydro-5H-inden-5-one (**31**).* Lithium metal (1.25 g, 180 mmol, 4.5 equiv) was added portionwise to freshly condensed ammonia (250 mL) at −78 °C, whereupon the mixture turned deep blue. After 30 min, a solution of 5-methoxyindan (**22**) (5.92 g, 40.0 mmol, 1.0 equiv) in THF (30 mL) was added dropwise at −78 °C. The mixture was then slowly warmed to −40 °C over a period of 3 h, whereupon ethanol (30 mL) was added, after which the blue color faded. The cooling bath was then removed, and the ammonia was allowed to evaporate overnight. The resulting residue was partitioned between water (200 mL) and diethyl ether (100 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (4 × 50 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 40 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered, and the filtrate was concentrated in vacuo. The crude enol ether (6.25 g yellow oil, ≥99%) was used in the next step without further purification. A portion of the crude enol ether (4.50 g, 30.0 mmol, 1.0 equiv) in methanol (80 mL) and water (40 mL) was treated with oxalic acid (6.78 g, 75.0 mmol, 2.5 equiv) at 0 °C. After 20 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (200 mL) and diethyl ether (70 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 50 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 50 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered, and the filtrate was concentrated in vacuo. The crude ketone **30** was used in the next step without further purification. Based on a slight modification of Deng's method,[26] a

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J. Org. Chem. 2019, 84, 14069−14091

solution of the crude ketone **30** (assuming 30.0 mmol) in chloroform (60 mL) was treated with cinchona alkaloid catalyst **QD** (2.17 g, 4.50 mmol, 15 mol %) and (*R*)-2-chloropropionic acid (977 mg, 9.00 mmol, 30 mol %) at −20 °C. After stirring for 10 days at this temperature, the mixture was directly purified by flash column chromatography (40% → 60% diethyl ether in pentane) to give enone **31** (2.04 g, 15.0 mmol, 50% over 2 steps, 57% ee) as a yellow oil. TLC (10% diethyl ether in pentane): R_f = 0.31 (UV/$KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 5.86 (d, J = 2.3 Hz, 1H), 2.65−2.55 (m, 1H), 2.55−2.48 (m, 1H), 2.48−2.37 (m, 2H), 2.31−2.23 (m, 1H), 2.23−2.16 (m, 1H), 2.09−2.02 (m, 1H), 1.91−1.83 (m, 1H), 1.72−1.63 (m, 1H), 1.62−1.53 (m, 1H), 1.21 (qd, J = 11.9, 7.2 Hz, 1H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 199.9, 175.6, 122.3, 43.2, 37.5, 32.9, 31.9, 29.3, 23.9. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2947 (m), 2862 (m), 1657 (s), 1318 (m), 1240 (m), 1213 (m), 1183 (m), 867 (s). HRMS (ESI): calcd for ([M + H] $C_9H_{13}O)^+$, 137.0961; found, 137.0968. $[\alpha]_D^{20}$ = +0.1° (c = 1.0, CH_2Cl_2).

*Synthesis of (R)-2,6,7,7a-Tetrahydro-1H-inden-5-yl Trifluoromethanesulfonate (**32**).* A solution of enone **31** (57% ee, 690 mg, 5.07 mmol, 1.0 equiv) in THF (30 mL) was treated with potassium bis(trimethylsilyl)amide solution (0.7 M in PhMe, 6.12 mL, 4.31 mmol, 0.85 equiv) at −15 °C. The resulting dark orange mixture was then warmed to 23 °C. After 30 min, the mixture was cooled to 0 °C, whereupon *N*-phenyl-bis(trifluoromethanesulfonimide) (2.17 g, 6.08 mmol, 1.2 equiv) was added in one portion. After 5 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (50 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (100% hexanes) to give triflate **32** (1.16 g, 4.31 mmol, 85%) as a colorless oil. TLC (100% hexanes): R_f = 0.36 (UV/$KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.30 (d, J = 2.5 Hz, 1H), 5.71 (d, J = 2.9 Hz, 1H), 2.70−2.59 (m, 2H), 2.45−2.36 (m, 3H), 2.20−2.13 (m, 1H), 2.13−2.06 (m, 1H), 1.49−1.42 (m, 1H), 1.42−1.34 (m, 1H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 151.6, 139.3, 129.1, 118.7 (q, J = 380.9 Hz), 115.7, 42.4, 33.1, 31.0, 29.1, 29.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.04. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2931 (w), 2844 (w), 1416 (s), 1246 (m), 1201 (s), 1138 (s), 1043 (s), 1027 (s), 888 (m), 860 (s). HRMS (EI): calcd for ([M], $C_{10}H_{11}F_3O_3S)^+$: 268.0376; found, 268.0383. $[\alpha]_D^{20}$ = +10.6° (c = 2.2, CH_2Cl_2).

*Synthesis of (R)-2,6,7,7a-Tetrahydro-1H-indene-5-carboxylic Acid (**33**).* A solution of triflate **32** (1.16 g, 4.31 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (20 mL) was treated with pyridine (730 μL, 9.05 mmol, 2.1 equiv), tetrabutylammonium chloride (1.32 g, 4.74 mmol, 1.1 equiv), and palladium(II) acetate (96.8 mg, 0.43 mmol, 0.1 equiv) at 23 °C. The reaction mixture was sparged with carbon monoxide gas for 15 min, and stirring was then continued under 1 atm carbon monoxide pressure (balloon) at 60 °C. After 16 h, the mixture was cooled to 23 °C and was diluted with saturated aqueous ammonium chloride solution (70 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (4 × 40 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to give carboxylic acid **33** (531 mg, 3.23 mmol, 75%, 53% ee) as a white solid. TLC (40% ethyl acetate in hexanes): R_f = 0.44 (UV/$KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.44 (d, J = 2.6 Hz, 1H), 5.97 (d, J = 2.8 Hz, 1H), 2.68−2.58 (m, 2H), 2.48−2.40 (m, 2H), 2.35−2.26 (m, 1H), 2.24−2.16 (m, 1H), 2.13−2.08 (m, 1H), 1.46−1.38 (m, 1H), 1.25 (qd, J = 12.5, 4.9 Hz, 1H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 173.6, 142.7, 134.5, 133.7, 129.8, 42.8, 32.8, 31.8, 29.4, 25.3. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3275 (br), 3073 (m), 1656 (s), 1376 (s), 1206 (s), 1141 (s), 602 (s). HRMS (ESI): calcd for ([M − H] $C_{10}H_{11}O_2)^-$, 163.0765; found, 163.0762. $[\alpha]_D^{20}$ = +75.2° (c = 1.1, CH_2Cl_2). mp 180−185 °C.

*Synthesis of (E)-2-((3S,4S)-1-Allyl-3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-methylpyrrolidin-2-ylidene)-1-((R)-2,6,7,7a-tetrahydro-1H-inden-5-yl)ethan-1-one (**36**).* A mixture of carboxylic acid **33** (53% ee, 460 mg, 2.80 mmol, 1.2 equiv) in dichloromethane (23 mL) and *N*,*N*-dimethylformamide (4 drops) was treated dropwise with oxalyl chloride (280 μL, 3.27 mmol, 1.4 equiv) at 0 °C. The resulting mixture was warmed to 23 °C, whereupon it turned into a clear, orange solution. After 2 h, the mixture was concentrated in vacuo to give acid chloride **34** which was used in the next step without further purification. A flask was charged with acid chloride **34** (assuming 2.80 mmol), bis(triphenylphosphine)palladium(II) dichloride (81.8 mg, 0.12 mmol, 5 mol %), and copper(I) iodide (44.4 mg, 0.23 mmol, 10 mol %). A solution of amide **29** (911 mg, 2.33 mmol, 1.0 equiv) in triethylamine (20 mL) was then added at 23 °C. After 30 min, the mixture was diluted with water (40 mL) and diethyl ether (30 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was used in the next step without further purification. The crude alkynone (assuming 2.80 mmol) in methanol (17 mL), THF (5 mL) and water (5 mL) was treated with potassium carbonate (966 mg, 6.99 mmol, 3.0 equiv) at 0 °C. The resulting mixture was then warmed to 23 °C. After 18 h, the mixture was diluted with saturated aqueous sodium bicarbonate solution (50 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (4 × 40 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (10% → 20% ethyl acetate in hexanes) to give vinylogous amide **36** (701 mg, 1.59 mmol, 68% over three steps, ∼3:1 d.r. at C10) as an orange oil. TLC (15% ethyl acetate in hexanes): R_f = 0.36 (UV/$KMnO_4$). *Note*: As a result of the low enantiomeric purity of carboxylic acid **33** (53% ee), vinylogous amide **36** was obtained as an inseparable mixture of diastereomers (∼3:1 d.r. at C10). In cases where the proton or carbon atoms show a double set of signals, the signal of the minor diastereomer is marked with an asterisk. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.99 (s, 1H), 6.98* (s, 1H), 5.79−5.72 (m, 2H), 5.43* (s, 1H), 5.42 (s, 1H), 5.26−5.15 (m, 2H), 3.90−3.78 (m, 4H), 3.76−3.70 (m, 1H), 3.58−3.51 (m, 1H), 2.88 (d, J = 10.3 Hz, 1H), 2.74* (dd, J = 17.9, 4.7 Hz, 1H), 2.68−2.56 (m, 2H), 2.48−2.31 (m, 4H), 2.19−2.12 (m, 1H), 2.11−2.05 (m, 1H), 1.89−1.83 (m, 1H), 1.61−1.54 (m, 2H), 1.43−1.34 (m, 1H), 1.25−1.18 (m, 1H), 0.98 (d, J = 7.1 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 188.59, 188.56*, 169.3, 169.2*, 144.0*, 143.9, 142.9*, 142.8, 130.9*, 130.8, 128.6, 128.5*, 125.5, 125.5*, 117.7, 117.7*, 86.2*, 86.2, 63.7, 58.1, 58.1*, 51.2, 51.1*, 49.0, 43.4*, 43.4, 35.2, 35.1*, 34.0*, 33.9, 32.6*, 32.6, 32.0, 31.9*, 30.1, 26.3, 26.1, 26.0*, 21.1, 18.4, −5.2. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3349 (br), 2952 (m), 2927 (s), 2855 (m), 1672 (m), 1531 (s), 1472 (m), 1461 (m), 1253 (m), 1200 (m), 1092 (s), 833 (s), 775 (s). HRMS (ESI): calcd for ([M + H] $C_{27}H_{44}NO_2Si)^+$, 442.3136; found, 442.3125. $[\alpha]_D^{20}$ = +69.8° (c = 0.57, CH_2Cl_2).

*Synthesis of (5S,6S)-4-Allyl-5-(2-((tert-butyldimethylsilyl)oxy)-ethyl)-1,1-diethyl-6-methyl-3-((R)-2,6,7,7a-tetrahydro-1H-inden-5-yl)-1,5,6,7-tetrahydro-1λ^4,8λ^4-pyrrolo[1,2-c][1,3,2]oxazaborinine (**40**).* Following the developed procedure,[34] an oven-dried vial was charged with vinylogous amide **36** (40 mg, 90.6 μmol, 1.0 equiv, 3:1 d.r. at C10), pyridinium *p*-toluenesulfonate (2.3 mg, 9.06 μmol, 10 mol %), triphenylphosphine (3.6 mg, 13.6 μmol, 15 mol %), and palladium(II) acetate (1.4 mg, 6.34 μmol, 7 mol %). The vial was flushed with nitrogen and sealed with a septum cap. Toluene (0.5 mL) and a solution of triethylborane (1 M in THF, 137 μL, 137 μmol, 1.5 equiv) were added sequentially, and the vial was placed in a preheated (80 °C) heating block. After 1 h, the mixture was cooled to 23 °C and concentrated in vacuo, and the crude residue was purified by flash column chromatography (0% → 2% ethyl acetate in hexanes)

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J. Org. Chem. 2019, 84, 14069−14091

to give oxazaborinine **40** (36 mg, 70.7 μmol, 78%, ~3:1 d.r. at C10) as an orange oil. TLC (2% ethyl acetate in hexanes): R_f = 0.27 (UV/$KMnO_4$). *Note*: Oxazaborinine **40** was obtained as an inseparable mixture of diastereomers (~3:1 d.r. at C10). In cases where the proton or carbon atoms show a double set of signals, the signal of the minor diastereomer is marked with an asterisk. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.42−6.37 (m, 1H), 5.93−5.82 (m, 1H), 5.57 (s, 1H), 5.11−4.98 (m, 2H), 3.76−3.58 (m, 3H), 3.19−3.00 (m, 2H), 2.87−2.81 (m, 1H), 2.77 (d, *J* = 10.7 Hz, 1H), 2.66−2.56 (m, 1H), 2.53−2.28 (m, 4H), 2.21−2.09 (m, 2H), 2.07−2.00 (m, 1H), 1.77−1.70 (m, 1H), 1.51−1.43 (m, 1H), 1.39−1.20 (m, 2H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.83−0.74 (m, 6H), 0.41−0.28 (m, 4H), 0.08−0.02 (m, 6H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 176.42, 176.39*, 175.8, 175.6*, 142.8*, 142.7, 139.20*, 139.18, 137.3, 137.2*, 126.53, 126.51*, 123.8, 123.6*, 114.69, 114.66*, 96.4*, 96.2, 61.1, 58.3, 50.9, 43.1*, 43.1, 34.14*, 34.10, 33.6, 32.2, 32.0, 31.9*, 31.1*, 31.0, 29.9, 28.0, 27.6*, 26.1*, 26.0, 20.7, 18.4, 14.4 (br), 9.33, 9.26, −5.27, −5.32. ^{11}B NMR (128 MHz, $CDCl_3$): δ 7.33. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2928 (s), 2857 (s), 1614 (m), 1501 (m), 1460 (s), 1254 (s), 1095 (s), 1029 (m), 832 (s), 812 (m), 774 (s). HRMS (ESI): calcd for ([M + H] $C_{31}H_{53}BNO_2Si)^+$, 510.3933; found, 510.3924. $[\alpha]_D^{20}$ = −20.6° (*c* = 0.77, CH_2Cl_2).

*Synthesis of (S)-2-(1-((Trimethylsilyl)ethynyl)cyclopropyl)-propan-1-ol (**50**) via Hydroboration−Oxidation.* According to Fürstner's method,[44] isopropenylmagnesium bromide solution (0.5 M in THF, 10.1 mL, 5.07 mmol, 1.3 equiv) was added slowly to a mixture of tosylate **48** (1.20 g, 3.90 mmol, 1.0 equiv) and iron(III) acetylacetonate (68.9 mg, 0.20 mmol, 5 mol %) in THF (35 mL) at −30 °C. After 10 min, the mixture was diluted with saturated aqueous ammonium chloride solution (50 mL) and diethyl ether (30 mL). The layers were separated, the aqueous layer was extracted diethyl ether (2 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (40 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was filtered through a short pad of silica, eluting with diethyl ether (20 mL). The filtrate was concentrated in vacuo to give spectroscopically pure (^{1}H NMR) alkene **49** (642 mg, 3.60 mmol, 92%) as a yellowish oil that was used in the next step without further purification. According to Yun's method,[43] a mixture of copper(I) chloride (3.4 mg, 34.8 μmol, 5 mol %), (*S*)-DTBM-SEGPHOS (45 mg, 38.2 μmol, 6 mol %), and potassium *tert*-butoxide (16 mg, 139 μmol, 0.2 equiv) in toluene (0.5 mL) were stirred for 5 min under an atmosphere of nitrogen at 23 °C. Pinacolborane (121 μL, 835 μmol, 1.2 equiv) was added, and after further 15 min, a solution of alkene **49** (0.13 g, 0.70 mmol, 1.0 equiv) in toluene (0.7 mL) was added. After 9 h, the mixture was filtered through a pad of Celite, eluting with ethyl acetate (10 mL). The filtrate was concentrated in vacuo, and the residue was used in the next step without further purification. A solution of the crude residue in THF (2 mL) and water (2 mL) was treated with sodium perborate tetrahydrate (0.32 g, 2.07 mmol, 3.0 equiv) at 23 °C. After 5 h, the mixture was diluted with water (10 mL) and ethyl acetate (10 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to give alcohol **50** (12 mg, 61.1 μmol, 9%) as a colorless liquid. The ^{1}H, ^{13}C{^{1}H} spectra and HRMS data of **50** were in full agreement with the values reported for alcohol **50** prepared via the auxiliary-based approach (see below). Based on the low isolated yield, the enantiomeric excess of **50** prepared via this hydroboration/oxidation sequence was not determined.

*Synthesis of 2-(1-((Trimethylsilyl)ethynyl)cyclopropyl)acetic Acid (**51**).* A solution of cyclopropyl(trimethylsilyl)acetylene (13.8 g, 100 mmol, 1.0 equiv) in diethyl ether (170 mL) was treated with *n*-butyllithium solution (2.5 M in hexanes, 40 mL, 100 mmol, 1.0 equiv) at −78 °C. The resulting mixture was then allowed to warm to 23 °C overnight. After 17 h, the mixture was cooled to −78 °C, whereupon a solution of freshly condensed oxirane (ca. 6.51 mL, 130 mmol, 1.3 equiv) in diethyl ether (15 mL) was slowly added. The resulting mixture was then warmed to 0 °C. After 30 min, the mixture was diluted with saturated aqueous ammonium chloride solution (100 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 40 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The residue was used in the next step without further purification. A solution of dimethyl sulfoxide (21.3 mL, 300 mmol, 3.0 equiv) in dichloromethane (50 mL) was slowly added to oxalyl chloride (17.1 mL, 200 mmol, 2.0 equiv) in dichloromethane (250 mL) at −78 °C. After 15 min, a solution of the crude alcohol (assuming 100 mmol) in dichloromethane (75 mL) was slowly added at this temperature. After 15 min, triethylamine (55.5 mL, 400 mmol, 4.0 equiv) was added, and after further 15 min, the mixture was warmed to 0 °C. After 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (200 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The residue was used in the next step without further purification. A solution of the crude aldehyde (assuming 100 mmol) in acetone (340 mL) and water (100 mL) was treated sequentially with 2-methylbut-2-ene (53 mL, 500 mmol, 5.0 equiv), sodium phosphate monobasic monohydrate (31.7 g, 230 mmol, 2.3 equiv), and sodium chlorite 27.1 g, 300 mmol, 3.0 equiv) at 0 °C. The resulting mixture was then warmed to 23 °C. After 2 h, the mixture was concentrated to approximately half its volume and diluted with aqueous 1 M hydrogen chloride solution (200 mL) and dichloromethane (100 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 × 40 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (30% → 50% ethyl acetate in hexanes) to give cyclopropyl acid **51** (17.6 g, 90.0 mmol, 90% over 3 steps) as a yellow oil. TLC (50% ethyl acetate in hexanes): R_f = 0.40 ($KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.44 (s, 2H), 1.07−1.04 (m, 2H), 0.81−0.79 (m, 2H), 0.11 (s, 9H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 177.4, 109.9, 81.5, 42.7, 16.0, 9.5, 0.3. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3092 (br), 2958 (m), 2163 (m), 1710 (s), 1410 (m), 1248 (s), 867 (m), 836 (s), 758 (s). HRMS (ESI): calcd for ([M + Na] $C_{10}H_{16}NaO_2Si)^+$, 219.0812; found, 219.0808.

*Synthesis of (S)-4-Benzyl-3-(2-(1-((trimethylsilyl)ethynyl)-cyclopropyl)acetyl)oxazolidin-2-one (**S108**).* A solution of cyclopropyl acid **51** (7.84 g, 40.0 mmol, 1.0 equiv) in THF (200 mL) was treated sequentially with triethylamine (6.65 mL, 48.0 mmol, 1.2 equiv) and pivaloyl chloride (5.41 mL, 44.0 mmol, 1.1 equiv) at −78 °C. The resulting suspension was then warmed to 0 °C. After 30 min, in a separate flask, a solution of (*S*)-4-benzyl-2-oxazolidinone (7.80 g, 44.0 mmol, 1.1 equiv) in THF (200 mL) was treated with *n*-butyllithium solution (2.5 M in hexanes, 17.6 mL, 44.0 mmol, 1.1 equiv) at −78 °C. After 30 min, the mixture containing the intermediate anhydride was cooled to −78 °C, whereupon the mixture containing the lithiated oxazolidinone was added via cannula. The resulting mixture was warmed to 23 °C. After 50 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (200 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 40 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (20% → 30% ethyl acetate in hexanes) to give oxazolidinone **S108** (11.4 g, 32.1 mmol, 80%) as a yellow solid.

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TLC (20% ethyl acetate in hexanes): R_f = 0.25 (UV/$KMnO_4$). ^1H NMR (700 MHz, $CDCl_3$): δ 7.35−7.31 (m, 2H), 7.29−7.26 (m, 1H), 7.24−7.21 (m, 2H), 4.76−4.69 (m, 1H), 4.23−4.19 (m, 1H), 4.18 (dd, J = 9.0, 3.1 Hz, 1H), 3.33 (dd, J = 13.4, 3.2 Hz, 1H), 3.11 (d, J = 17.0 Hz, 1H), 3.01 (d, J = 17.0 Hz, 1H), 2.82 (dd, J = 13.4, 9.5 Hz, 1H), 1.14−1.06 (m, 2H), 0.86−0.77 (m, 2H), 0.11 (s, 9H). $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 170.7, 153.6, 135.4, 129.6, 129.1, 127.5, 110.4, 80.7, 66.4, 55.3, 43.5, 37.9, 16.1, 15.9, 9.5, 0.3. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3026 (w), 2958 (m), 2161 (m), 1775 (s), 1705 (s), 1385 (s), 1371 (s), 1248 (m), 1210 (s), 838 (s), 759 (s), 698 (s). HRMS (ESI): calcd for ([M + Na] $C_{20}H_{25}NNaO_3Si)^+$, 378.1496; found, 378.1490. $[\alpha]_D^{20}$ = +76.2° (c = 1.0, CH_2Cl_2). mp 73−77 °C.

*Synthesis of (S)-4-Benzyl-3-((S)-2-(1-((trimethylsilyl)ethynyl)-cyclopropyl)propanoyl)oxazolidin-2-one (**52**).* A solution of oxazolidinone **S108** (6.30 g, 17.7 mmol, 1.0 equiv) in THF (100 mL) was treated with sodium bis(trimethylsilyl)amide solution (2 M in THF, 10.6 mL, 21.2 mmol, 1.2 equiv) at −78 °C. After 50 min, methyl iodide (1.65 mL, 26.6 mmol, 1.5 equiv) was added. After 45 min, the mixture was warmed to 0 °C. After further 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (100 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 40 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (70 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (5% → 20% ethyl acetate in hexanes) to give methylated oxazolidinone **52** (5.16 g, 13.9 mmol, 79%) as a yellow solid. TLC (20% ethyl acetate in hexanes): R_f = 0.32 (UV/$KMnO_4$). ^1H NMR (700 MHz, $CDCl_3$): δ 7.35−7.30 (m, 2H), 7.29−7.25 (m, 1H), 7.23−7.20 (m, 2H), 4.73−4.68 (m, 1H), 4.22−4.14 (m, 2H), 3.47 (q, J = 6.9 Hz, 1H), 3.31 (dd, J = 13.5, 3.3 Hz, 1H), 2.79 (dd, J = 13.4, 9.5 Hz, 1H), 1.35 (d, J = 7.0 Hz, 3H), 1.00−0.95 (m, 2H), 0.91−0.84 (m, 1H), 0.81−0.75 (m, 1H), 0.14 (s, 9H). $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 174.5, 153.4, 135.4, 129.6, 129.0, 127.5, 109.7, 82.1, 66.2, 55.7, 42.8, 37.9, 15.9, 15.7, 15.2, 14.6, 0.4. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2959 (w), 2159 (m), 1774 (s), 1703 (s), 1382 (s), 1247 (m), 1207 (s), 841 (s), 760 (m), 700 (m). HRMS (ESI): calcd for ([M + Na] $C_{21}H_{27}NNaO_3Si)^+$, 392.1647; found, 392.1659. $[\alpha]_D^{20}$ = +25.1° (c = 1.0, CH_2Cl_2). mp 70−75 °C.

*Synthesis of (S)-2-(1-((Trimethylsilyl)ethynyl)cyclopropyl)-propan-1-ol (**50**).* A solution of methylated oxazolidinone **52** (3.99 g, 10.8 mmol, 1.0 equiv) in THF (100 mL) was treated with methanol (0.87 mL, 21.8 mmol, 2.0 equiv) and lithium borohydride (470 mg, 21.6 mmol, 2.0 equiv) at 0 °C. After 2 h, the mixture was diluted with saturated aqueous ammonium chloride solution (50 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 30 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (5% → 30% ethyl acetate in hexanes) to give alcohol **50** (2.01 g, 10.3 mmol, 85%) as a colorless liquid. TLC (20% ethyl acetate in hexanes): R_f = 0.27 ($KMnO_4$). ^1H NMR (700 MHz, $CDCl_3$): δ 3.79−3.73 (m, 1H), 3.69−3.62 (m, 1H), 1.79 (br s, 1H), 1.07 (d, J = 6.8 Hz, 3H), 1.01−0.91 (m, 2H), 0.89−0.84 (m, 1H), 0.75 (ddd, J = 9.2, 6.4, 4.2 Hz, 1H), 0.55 (ddd, J = 9.2, 6.4, 4.2 Hz, 1H), 0.13 (s, 9H). $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 109.6, 82.8, 67.3, 43.4, 16.1, 15.6, 14.8, 14.0, 0.3. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3330 (br), 2959 (m), 2875 (w), 2157 (m), 1248 (s), 1027 (s), 836 (s), 758 (s). HRMS (ESI): calcd for ([M + Na] $C_{11}H_{20}NaOSi)^+$, 219.1176; found, 219.1177. $[\alpha]_D^{20}$ = +2.0° (c = 1.0, CH_2Cl_2).

*Synthesis of (S)-2-(1-Ethynylcyclopropyl)propyl Methanesulfonate (**53**).* A solution of alcohol **50** (1.83 g, 9.33 mmol, 1.0 equiv) in dichloromethane (50 mL) was treated sequentially with triethylamine (3.23 mL, 23.3 mmol, 2.5 equiv) and methanesulfonyl chloride (867 μL, 11.2 mmol, 1.2 equiv) at 0 °C. After 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (30 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The residue was used in the next step without further purification. A solution of the crude silyl mesylate (assuming 9.33 mmol) in THF (50 mL) was treated with TBAF solution (1 M in THF, 12.1 mL, 12.1 mmol, 1.3 equiv) at 0 °C. After 5 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (30 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (10% → 20% ethyl acetate in hexanes) to give mesylate **53** (1.81 g, 8.96 mmol, 96% over 2 steps) as a colorless liquid. TLC (30% ethyl acetate in hexanes): R_f = 0.33 ($KMnO_4$). ^1H NMR (700 MHz, $CDCl_3$): δ 4.35 (dd, J = 9.9, 7.3 Hz, 1H), 4.16 (dd, J = 9.9, 7.0 Hz, 1H), 3.03 (s, 3H), 1.90 (s, 1H), 1.25−1.17 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H), 1.02−0.97 (m, 1H), 0.91 (ddd, J = 9.5, 6.5, 4.4 Hz, 1H), 0.80 (ddd, J = 9.3, 6.5, 4.5 Hz, 1H), 0.58 (ddd, J = 9.3, 6.6, 4.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 85.7, 73.2, 67.0, 40.6, 37.4, 15.7, 14.7, 14.4, 13.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3281 (m), 2970 (w), 2938 (w), 1458 (w), 1349 (s), 1171 (s), 958 (s), 916 (m), 834 (s). HRMS (ESI): calcd for ([M + Na] $C_9H_{14}NaO_3S)^+$, 225.0556; found, 225.0554. $[\alpha]_D^{20}$ = −17.3° (c = 1.0, CH_2Cl_2).

*Synthesis of (S)-N-Allyl-N-(2-(1-ethynylcyclopropyl)propyl)-2,2,2-trifluoroacetamide (**56**).* A solution of mesylate **53** (700 mg, 3.46 mmol, 1.0 equiv) in acetonitrile (1.7 mL) was treated with triethylamine (591 μL, 4.15 mmol, 1.2 equiv), allylamine (3.90 mL, 51.9 mmol, 15 equiv), and sodium iodide (779 mg, 5.19 mmol, 1.5 equiv) at 23 °C. The resulting mixture was heated to 45 °C. After 48 h, the mixture was cooled to 23 °C and then was filtered through a pad of Celite, eluting with ethyl acetate (100 mL). The filtrate was concentrated in vacuo, and the residue was used in the next step without further purification. A solution of the crude secondary amine (assuming 3.46 mmol) in dichloromethane (35 mL) was treated sequentially with triethylamine (1.92 mL, 13.8 mmol, 4.0 equiv) and trifluoroacetic anhydride (963 μL, 6.92 mmol, 2.0 equiv) at −78 °C. After 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (50 mL) and warmed to 23 °C. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give amide **56** (513 mg, 1.98 mmol, 57% over 2 steps) as a colorless oil. TLC (10% ethyl acetate in hexanes): R_f = 0.49 ($KMnO_4$). *Note*: As determined by NMR spectroscopy, amide **56** exists as a mixture of rotamers (4:1 ratio) at 23 °C. In cases where the proton or carbon atoms show a double set of signals, the signal of the minor rotamer is marked with an asterisk. ^1H NMR (700 MHz, $CDCl_3$): δ 5.80−5.70 (m, 1H), 5.29−5.18 (m, 2H), 4.43−4.36* (m, 1H), 4.24−4.11 (m, 2H), 3.87* (dd, J = 15.1, 7.0 Hz, 1H), 3.62−3.51 (m, 1H), 3.46−3.39* (m, 1H), 3.24 (dd, J = 13.6, 9.1 Hz, 1H), 1.93 (s, 1H), 1.36−1.28 (m, 1H), 1.09−1.02 (m, 3H), 1.01−0.91 (m, 1H), 0.91−0.84 (m, 1H), 0.68−0.61 (m, 1H), 0.58−0.54* (m, 1H), 0.52−0.46 (m, 1H). $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 157.1 (q, J = 35.6 Hz), 132.2, 131.3*, 119.0, 118.6*, 116.5 (q, J = 287.9 Hz), 86.5, 85.7*, 67.4*, 67.2, 51.4 (q, J = 3.3 Hz), 51.3, 50.3* (q, J = 2.9 Hz), 50.0*, 41.0*, 38.3, 16.4, 15.74*, 15.71*, 15.41, 15.38*, 15.26, 14.3*, 13.4. ^{19}F NMR (376 MHz, CDCl3): δ −67.48*, −68.52. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3310 (w), 2969 (w), 1685 (s), 1454 (m), 1285 (m), 1203 (s), 1169 (s), 1137 (s), 935 (m). HRMS (ESI): calcd for ([M + Na] $C_{13}H_{16}F_3NNaO)^+$, 282.1076; found, 282.1078. $[\alpha]_D^{20}$ = −113.1° (c = 1.0, CH_2Cl_2).

Synthesis of (S)-2-(1-(3-Oxo-3-((R)-2,6,7,7a-tetrahydro-1H-inden-5-yl)prop-1-yn-1-yl)cyclopropyl)propyl Methanesulfonate

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(54). A mixture of carboxylic acid **33** (53% ee, 400 mg, 2.44 mmol, 1.2 equiv) in dichloromethane (20 mL) and *N*,*N*-dimethylformamide (4 drops) was treated dropwise with oxalyl chloride (243 μL, 2.84 mmol, 1.4 equiv) at 0 °C. The resulting mixture was warmed to 23 °C, whereupon it turned into a clear, orange solution. After 2 h, the mixture was concentrated in vacuo to give acid chloride **34** which was used in the next step without further purification. A flask was charged with acid chloride **34** (assuming 2.44 mmol), bis(triphenylphosphine)palladium(II) dichloride (71.2 mg, 0.10 mmol, 5 mol %), and copper(I) iodide (38.7 mg, 0.20 mmol, 10 mol %). A solution of mesylate **53** (410 mg, 2.03 mmol, 1.0 equiv) in triethylamine (17 mL) was then added at 23 °C. After 30 min, the mixture was diluted with water (40 mL) and diethyl ether (30 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to give alkynone **54** (685 mg, 1.97 mmol, 97% over two steps, ∼3:1 d.r. at C10) as an orange oil. TLC (50% ethyl acetate in hexanes): R_f = 0.45 (UV/$KMnO_4$). *Note*: As a result of the low enantiomeric purity of carboxylic acid **33** (53% ee), alkynone **54** was obtained as an inseparable mixture of diastereomers (∼3:1 d.r. at C10). In cases where the proton or carbon atoms show a double set of signals, the signal of the minor diastereomer is marked with an asterisk. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.49 (br s, 1H), 6.15 (br s, 1H), 4.36 (dd, *J* = 10.0, 7.3 Hz, 1H), 4.24−4.19 (m, 1H), 3.04 (s, 3H), 2.72−2.61 (m, 2H), 2.49−2.43 (m, 2H), 2.23−2.05 (m, 3H), 1.47−1.37 (m, 1H), 1.37−1.30 (m, 1H), 1.25−1.10 (m, 6H), 1.04−0.97 (m, 1H), 0.81−0.76 (m, 1H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 179.1, 143.2, 140.3, 140.3*, 137.7, 136.11*, 136.10, 95.5, 77.79*, 77.77, 72.8, 43.2, 40.7, 37.5, 33.1, 31.8, 28.9, 23.93, 23.91*, 16.9, 15.17*, 15.16, 15.10*, 15.08. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2932 (m), 2857 (w), 2198 (s), 1627 (m), 1599 (s), 1352 (s), 1200 (m), 1172 (s), 960 (s), 888 (m), 833 (s). HRMS (ESI): calcd for ([M + Na] $C_{19}H_{24}NaO_4S)^+$, 371.1288; found, 371.1282. $[\alpha]_D^{20}$ = −8.9° (*c* = 1.7, CH_2Cl_2).

Synthesis of 2-((S)-5-Allyl-7-methyl-5-azaspiro[2.4]heptan-4-ylidene)-1-((R)-2,6,7,7a-tetrahydro-1H-inden-5-yl)ethan-1-one (55). A solution of alkynone **54** (2.09 g, 6.03 mmol, 1.0 equiv, ∼3:1 d.r. at C10) in acetonitrile (60 mL) was treated with triethylamine (1.00 mL, 7.24 mmol, 1.2 equiv) and allylamine (3.17 mL, 42.2 mmol, 7.0 equiv), and the resulting mixture was heated to 60 °C. After 26 h, the mixture was cooled to 23 °C and concentrated in vacuo. The crude residue was purified by flash column chromatography (40% → 50% ethyl acetate in hexanes) to give cyclopropyl vinylogous amide **55** (470 mg, 1.52 mmol, 25%, ∼3:1 d.r. at C10) as a dark red oil. TLC (50% ethyl acetate in hexanes): R_f = 0.30 (UV/$KMnO_4$). *Note*: Cyclopropyl vinylogous amide **55** was obtained as an inseparable mixture of diastereomers (∼3:1 d.r. at C10). In cases where the proton or carbon atoms show a double set of signals, the signal of the minor diastereomer is marked with an asterisk. Furthermore, **55** shows signal broadening in the ^{1}H and ^{13}C{^{1}H} NMR spectra, presumably because of hindered rotation. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.92 (s, 1H), 5.91−5.79 (m, 1H), 5.72 (s, 1H), 5.22−5.07 (m, 2H), 4.61 (br s, 1H), 4.43 (br s, 2H), 3.69 (t, *J* = 9.1 Hz, 1H), 3.18−3.09 (m, 1H), 2.69−2.51 (m, 2H), 2.43−2.33 (m, 2H), 2.33−2.21 (m, 1H), 2.18−2.09 (m, 2H), 2.09−1.99 (m, 1H), 1.43−1.31 (m, 1H), 1.19 (qd, *J* = 12.5, 4.8 Hz, 1H), 1.04−0.76 (m, 6H), 0.73 (br s, 1H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 187.4, 168.0, 143.9, 143.0, 133.2, 128.5, 125.9, 117.51, 117.48*, 81.6, 59.7, 54.4, 43.4, 34.6, 33.5, 32.6, 31.9, 30.0, 26.32, 26.28*, 15.9, 14.4, 11.4. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2922 (m), 2834 (m), 1604 (s), 1571 (m), 1523 (s), 1451 (m), 1427 (m), 1268 (m), 1199 (s), 914 (m). HRMS (ESI): calcd for ([M + H], $C_{21}H_{28}NO)^+$: 310.2165; found, 310.2164. $[\alpha]_D^{20}$ = +22.9° (*c* = 1.0, CH_2Cl_2).

Alternative Synthesis of 2-((S)-5-Allyl-7-methyl-5-azaspiro[2.4]heptan-4-ylidene)-1-((R)-2,6,7,7a-tetrahydro-1H-inden-5-yl)ethan-1-one (55). A mixture of carboxylic acid **33** (53% ee, 320 mg, 1.95 mmol, 1.1 equiv) in dichloromethane (17 mL) and *N*,*N*-dimethylformamide (3 drops) was treated dropwise with oxalyl chloride (190 μL, 2.21 mmol, 1.3 equiv) at 0 °C. The resulting mixture was warmed to 23 °C, whereupon it turned into a clear, orange solution. After 2 h, the mixture was concentrated in vacuo to give acid chloride **34** which was used in the next step without further purification. A flask was charged with acid chloride **34** (assuming 1.95 mmol), bis(triphenylphosphine)palladium(II) dichloride (62.1 mg, 88.5 μmol, 5 mol %), and copper(I) iodide (33.7 mg, 0.18 mmol, 10 mol %). A solution of amide **56** (459 mg, 1.77 mmol, 1.0 equiv) in triethylamine (15 mL) was then added at 23 °C. After 30 min, the mixture was diluted with water (40 mL) and diethyl ether (30 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was used in the next step without further purification. The crude alkynone (assuming 1.77 mmol) in methanol (15 mL), THF (5 mL) and water (5 mL) was treated with potassium carbonate (734 mg, 5.31 mmol, 3.0 equiv) at 0 °C. The resulting mixture was then warmed to 23 °C. After 18 h, the mixture was diluted with saturated aqueous sodium bicarbonate solution (50 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (4 × 40 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (20% → 50% ethyl acetate in hexanes) to give cyclopropyl vinylogous amide **55** (218 mg, 0.71 mmol, 40% over three steps, ∼3:1 d.r. at C10) as a yellow oil. The characterization data of **55** were in full agreement with the values reported above.

Synthesis of (S)-4′-Allyl-1′,1′-diethyl-6′-methyl-3′-((R)-2,6,7,7a-tetrahydro-1H-inden-5-yl)-6′,7′-dihydro-1′H-1′λ^4,8′λ^4-spiro[cyclopropane-1,5′-pyrrolo[1,2-c][1,3,2]oxazaborinine] (47). Following the developed procedure,[34] an oven-dried vial was charged with a magnetic stirring bar, cyclopropyl vinylogous amide **55** (100 mg, 324 μmol, 1.0 equiv, ∼3:1 d.r. at C10), pyridinium *p*-toluenesulfonate (8.1 mg, 32.4 μmol, 10 mol %), triphenylphosphine (8.5 mg, 32.4 μmol, 10 mol %), and palladium(II) acetate (3.6 mg, 16.2 μmol, 5 mol %). The vial was flushed with nitrogen and sealed with a septum cap. Toluene (1.5 mL) and a solution of triethylborane (1 M in THF, 486 μL, 486 μmol, 1.5 equiv) were added sequentially, and the vial was placed in a preheated (80 °C) heating block. After 1 h, the mixture was cooled to 23 °C and concentrated in vacuo, and the crude residue was purified by flash column chromatography (1% → 3% ethyl acetate in hexanes) to give cyclopropyl oxazaborinine **47** (74 mg, 196 μmol, 60%, ∼3:1 d.r. at C10) as a yellow oil. TLC (4% ethyl acetate in hexanes): R_f = 0.48 (UV/$KMnO_4$). *Note*: Cyclopropyl oxazaborinine **47** was obtained as an inseparable mixture of diastereomers (∼3:1 d.r. at C10). In cases where the proton or carbon atoms show a double set of signals, the signal of the minor diastereomer is marked with an asterisk. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.29 (s, 1H), 5.91−5.80 (m, 1H), 5.53 (s, 1H), 5.10−5.02 (m, 2H), 3.71 (dd, *J* = 13.6, 7.4 Hz, 1H), 3.17 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.81−2.73 (m, 1H), 2.64−2.55 (m, 2H), 2.41−2.29 (m, 4H), 2.15−2.09 (m, 1H), 2.05−1.99 (m, 1H), 1.99−1.93 (m, 1H), 1.39−1.22 (m, 4H), 0.97−0.88 (m, 4H), 0.85−0.74 (m, 7H), 0.41−0.32 (m, 4H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 176.2, 176.1*, 173.8, 142.6, 139.5, 137.6, 126.1, 123.13, 123.08*, 115.2, 95.5, 56.8, 43.1*, 43.1, 37.50*, 37.49, 35.83, 35.82*, 32.2, 31.94, 31.93*, 29.9, 29.19*, 29.18, 28.2, 28.1*, 16.68, 16.66*, 14.0, 13.9*, 10.8, 9.39*, 9.37, 9.36, 9.35*. ^{11}B NMR (128 MHz, $CDCl_3$): δ 6.02. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2929 (m), 2859 (m), 1584 (s), 1482 (s), 1449 (s), 1330 (m), 1300 (s), 1200 (s), 1083 (m), 1053 (m), 911 (s). HRMS (ESI): calcd for ([M + Na] $C_{25}H_{36}BNNaO)^+$, 400.2782; found, 400.2784. $[\alpha]_D^{20}$ = −14.8° (*c* = 1.0, CH_2Cl_2).

Synthesis of (2S,7aR)-4-Allyl-2-methyl-1,2,7,7A,8,9-hexahydrospiro[cyclopenta[h]pyrrolo[1,2-a]quinoline-3,1′-cyclo-

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*propan]-5(6H)-one (**58**).* A solution of cyclopropyl oxazaborinine **47** (30.7 mg, 81.3 μmol, 1.0 equiv, ~3:1 d.r. at C10) in ethanol (1 mL) was treated with 4-(dimethylamino)pyridine (99.4 mg, 813 μmol, 10 equiv), and the resulting mixture was heated to 80 °C. After 20 h, the mixture was cooled to 23 °C and then was filtered through a short pad of silica, eluting with ethyl acetate (20 mL). The filtrate was concentrated in vacuo, and the residue was used in the next step without further purification. A solution of the crude α-allyl vinylogous amide (assuming 81.3 μmol) in *N*,*N*-dimethylformamide (0.1 mL) and *N*,*O*-bis(trimethylsilyl)acetamide (1 mL) was heated to 130 °C. After 24 h, the mixture was cooled to 23 °C and concentrated in vacuo. The crude residue was prepurified by flash column chromatography (5% methanol in dichloromethane) to give a brown residue (ca. 25 mg) that was further purified by preparative TLC (2% methanol in dichloromethane) to give 4-pyridone **58** (2.5 mg, 8.14 μmol, 10%, ~1.5:1 d.r. at C10) as a yellow oil. TLC (5% methanol in dichloromethane): R_f = 0.20 (UV/$KMnO_4$). *Note*: Pyridone **58** was obtained as an inseparable mixture of diastereomers (~1.5:1 d.r. at C10). In cases where the proton or carbon atoms show a double set of signals, the signal of the minor diastereomer is marked with an asterisk. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.20−6.14 (m, 1H), 5.98−5.88 (m, 1H), 5.00−4.91 (m, 2H), 4.47−4.38 (m, 1H), 3.99−3.93* (m, 1H), 3.86−3.79* (m, 1H), 3.41−3.29 (m, 1H), 3.04−2.83 (m, 3H), 2.62−2.56 (m, 2H), 2.56−2.44 (m, 2H), 2.27−2.18 (m, 1H), 2.16−2.08 (m, 1H), 1.95−1.87* (m, 1H), 1.69−1.62 (m, 1H), 1.56−1.48 (m, 1H), 1.37 (app qd, *J* = 12.6, 5.5 Hz, 1H), 1.19−1.12 (m, 1H), 1.10 (t, *J* = 8.3 Hz, 1H), 1.01* (d, *J* = 7.0 Hz, 2H), 0.98−0.87 (m, 4H), 0.81−0.73 (m, 1H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 177.4, 151.8, 150.6*, 138.5*, 138.3, 137.96, 137.95*, 137.5, 137.4*, 131.1, 124.49*, 124.46, 118.7*, 118.4, 114.5, 114.4*, 58.8, 58.2*, 46.3, 46.2*, 38.8, 36.0, 33.4, 31.7*, 31.0*, 30.8, 29.9*, 29.5, 29.4*, 26.8, 26.7*, 24.62*, 24.56, 17.7*, 15.3*, 13.5, 10.6, 10.5, 10.0*. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3350 (br), 2924 (m), 1600 (s), 1534 (s), 1489 (s), 1434 (m), 1242 (m), 1224 (m), 906 (m). HRMS (ESI): calcd for ([M + H] $C_{21}H_{26}NO)^+$, 308.2009; found, 308.2012. $[\alpha]_D^{20}$ = −18.0° (*c* = 0.8, CH_2Cl_2).

*Synthesis of (S)-2-Bromo-N-(1-phenylethyl)prop-2-en-1-amine (**63**).* A solution of (*S*)-(−)-1-phenylethylamine (17.9 mL, 139 mmol, 1.8 equiv) in THF (250 mL) was treated with potassium carbonate (11.8 g, 85.0 mmol, 1.1 equiv) at 23 °C. 2,3-Dibromopropene (8.00 mL, 77.3 mmol, 1.0 equiv) was then added over a 30 min period. After the end of addition, the resulting mixture was warmed to 66 °C. After 23 h, the mixture was diluted with water (150 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 50 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (10% → 20% ethyl acetate in hexanes) to give vinyl bromide **63** (17.9 g, 74.9 mmol, 97%) as a yellow oil. TLC (20% ethyl acetate in hexanes): R_f = 0.41 (UV/$KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.39−7.34 (m, 4H), 7.32−7.26 (m, 1H), 5.71 (br s, 1H), 5.59 (d, *J* = 1.8 Hz, 1H), 3.84 (q, *J* = 6.6 Hz, 1H), 3.40 (d, *J* = 15.2 Hz, 1H), 3.30 (d, *J* = 15.2 Hz, 1H), 1.83 (br s, 1H), 1.40 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 144.9, 133.9, 128.6, 127.2, 127.0, 117.8, 55.7, 55.2, 24.4. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2961 (w), 2922 (m), 2832 (w), 1625 (m), 1492 (m), 1449 (s), 1370 (m), 1123 (s), 891 (s), 760 (s), 698 (s). HRMS (ESI): calcd for ([M + H] $C_{11}H_{15}{}^{79}BrN)^+$, 240.0382; found, 240.0380. $[\alpha]_D^{20}$ = −37.4° (*c* = 1.0, CH_2Cl_2).

*Synthesis of tert-Butyl (R)-3-((2-bromoallyl) ((S)-1-phenylethyl)-amino)pent-4-enoate (**65**).* A solution of vinyl bromide **63** (2.95 g, 12.3 mmol, 1.1 equiv) in THF (12 mL) was treated with *n*-butyllithium solution (1.6 M in hexanes, 7.00 mL, 11.2 mmol, 1.0 equiv) at −78 °C. After 3 min, a solution of dienoate **64**[66] (1.90 g, 12.3 mmol, 1.1 equiv) in THF (6 mL) was added. After 20 min, the mixture was diluted with saturated aqueous ammonium chloride solution (20 mL) and warmed to 23 °C. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (1% → 2% ethyl acetate in hexanes) to give ester **65** (2.91 g, 7.39 mmol, 66%) as a yellow oil. TLC (10% ethyl acetate in hexanes): R_f = 0.50 (UV/$KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.39−7.36 (m, 2H), 7.33−7.28 (m, 2H), 7.25−7.21 (m, 1H), 6.02 (s, 1H), 5.86−5.79 (m, 1H), 5.54 (s, 1H), 5.16−5.10 (m, 2H), 4.03 (q, *J* = 6.9 Hz, 1H), 3.86−3.80 (m, 1H), 3.39−3.28 (m, 2H), 2.39−2.26 (m, 2H), 1.41−1.40 (m, 3H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 171.1, 143.9, 138.0, 134.5, 128.3, 127.8, 127.1, 117.3, 116.5, 80.4, 58.5, 57.8, 55.2, 38.4, 28.2, 18.6. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2975 (m), 2931 (w), 1725 (s), 1366 (s), 1144 (s), 1085 (m), 918 (s), 892 (s), 733 (s), 699 (s). HRMS (ESI): calcd for ([M + Na] $C_{20}H_{28}{}^{79}BrNNaO_2)^+$, 416.1196; found, 416.1196. $[\alpha]_D^{20}$ = +24.5° (*c* = 1.0, CH_2Cl_2).

*Synthesis of tert-Butyl (S)-3-((2-bromoallyl) ((S)-1-phenylethyl)-amino)-2-methylenepent-4-enoate (**66**).* *n*-Butyllithium solution (2.5 M in hexanes, 6.84 mL, 17.1 mmol, 2.5 equiv) was added dropwise to a solution of DIPA (2.49 mL, 17.8 mmol, 2.6 equiv) in THF (20 mL) at −78 °C. After 15 min, a solution of ester **65** (2.40 g, 6.84 mmol, 1.0 equiv) in THF (15 mL) was added via a syringe to the freshly prepared lithium diisopropylamide solution at −78 °C. After 30 min, 2-methoxyethoxymethyl chloride (1.56 mL, 13.7 mmol, 2.0 equiv) was added, and the resulting mixture was warmed to 0 °C. After 30 min, potassium *tert*-butoxide solution (1 M in THF, 13.7 mL, 13.7 mmol, 2.0 equiv) was added, and the resulting mixture was warmed to 23 °C. After 1 h, the mixture was diluted with saturated aqueous ammonium chloride solution (50 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (3% → 5% ethyl acetate in hexanes) to give enoate **66** (1.39 g, 3.42 mmol, 50%) as a yellow oil. TLC (10% ethyl acetate in hexanes): R_f = 0.56 (UV/$KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.33−7.27 (m, 4H), 7.24−7.21 (m, 1H), 6.16 (d, *J* = 1.3 Hz, 1H), 6.07−6.03 (m, 1H), 5.90 (ddd, *J* = 17.1, 10.2, 8.1 Hz, 1H), 5.76 (br s, 1H), 5.49 (q, *J* = 1.5 Hz, 1H), 5.16−5.06 (m, 2H), 4.37 (d, *J* = 8.2 Hz, 1H), 4.10 (q, *J* = 6.9 Hz, 1H), 3.47 (d, *J* = 17.2 Hz, 1H), 3.31 (d, *J* = 17.2 Hz, 1H), 1.46 (s, 9H), 1.40 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 166.3, 143.3, 143.0, 137.0, 135.0, 128.2, 127.1, 124.8, 117.7, 116.9, 80.9, 63.1, 58.0, 55.1, 28.2, 18.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2975 (m), 1711 (s), 1366 (s), 1270 (m), 1254 (m), 1142 (s), 1101 (m), 1083 (m), 909 (s), 732 (s), 699 (s). HRMS (ESI): calcd for ([M + H] $C_{21}H_{29}{}^{79}BrNO_2)^+$, 406.1379; found, 406.1376. $[\alpha]_D^{20}$ = +20.9° (*c* = 1.0, CH_2Cl_2).

*Synthesis of tert-Butyl (3aS,6R,6aS)-3-methylene-1-((S)-1-phenylethyl)octahydrocyclopenta[b]pyrrole-6-carboxylate (70) and tert-Butyl (3aS,6S,6aS)-3-methylene-1-((S)-1-phenylethyl)-octahydrocyclopenta[b]pyrrole-6-carboxylate (**C8-epi-70**).* According to Molander's method,[50] a flask was charged with enoate **66** (1.00 g, 2.47 mmol, 1.0 equiv), tetrahydroxydiboron (266 mg, 2.96 mmol, 1.2 equiv), copper(I) chloride (12.2 mg, 124 μmol, 5 mol %), sodium *tert*-butoxide (71.2 mg, 741 μmol, 0.3 equiv), and (2-biphenyl)-dicyclohexylphosphine (43.3 mg, 124 μmol, 5 mol %). Ethanol (25 mL) was then added, and the mixture was stirred vigorously at 23 °C. After 3 h, the mixture was filtered through a pad of Celite, eluting with ethyl acetate (70 mL). The filtrate was concentrated in vacuo, and the residue was used in the next step without further purification. A solution of the crude boronic acid **67** (assuming 2.47 mmol) in N_2-sparged (30 min) THF (30 mL) and aqueous 2 M sodium carbonate solution (5.5 mL) was treated with tetrakis(triphenylphosphine)-palladium(0) (199 mg, 173 μmol, 7 mol %), and the resulting mixture was heated to 70 °C. After 17 h, the mixture was cooled to 23 °C and diluted with saturated aqueous sodium bicarbonate solution (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were

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washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (5% → 10% ethyl acetate in hexanes) to give, in order of elution, major bicycle **70** (218 mg, 666 μmol, 27%, yellow solid) and minor bicycle **C8-*epi*-70** (24.2 mg, 74.1 μmol, 3%, yellow oil). Data for major bicycle **70**: **TLC** (10% ethyl acetate in hexanes): R_f = 0.39 ($KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.26 (m, 4H), 7.25−7.20 (m, 1H), 4.62−4.52 (m, 2H), 3.93−3.85 (m, 1H), 3.68 (q, *J* = 6.9 Hz, 1H), 3.41−3.30 (m, 1H), 3.14 (dq, *J* = 14.8, 2.1 Hz, 1H), 2.91−2.84 (m, 1H), 2.54 (dd, *J* = 12.3, 7.1 Hz, 1H), 2.47−2.37 (m, 1H), 2.29−2.19 (m, 1H), 1.79−1.70 (m, 1H), 1.52 (s, 9H), 1.45−1.41 (m, 3H), 1.31−1.21 (m, 1H).^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 174.3, 147.2, 143.6, 128.2, 127.8, 126.9, 101.3, 80.3, 76.2, 64.1, 63.4, 52.2, 43.8, 32.7, 28.5, 22.7, 19.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2973 (m), 2934 (w), 1720 (s), 1366 (s), 1144 (s), 701 (s). HRMS (ESI): calcd for ([M + H] $C_{21}H_{30}NO_2)^+$, 328.2271; found, 328.2274. $[\alpha]_D^{20}$ = −56.6° (*c* = 1.0, CH_2Cl_2). mp 65−70 °C. Data for minor bicycle **C8-*epi*-70**: **TLC** (20% ethyl acetate in hexanes): R_f = 0.38 (UV/$KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.33−7.28 (m, 4H), 7.24−7.21 (m, 1H), 4.64−4.52 (m, 2H), 3.72−3.64 (m, 1H), 3.50 (q, *J* = 6.6 Hz, 1H), 3.14 (dq, *J* = 15.0, 2.3 Hz, 1H), 2.92 (dd, *J* = 11.9, 9.3 Hz, 1H), 2.89−2.79 (m, 1H), 2.68−2.53 (m, 2H), 2.21−2.13 (m, 1H), 1.74−1.68 (m, 1H), 1.46 (s, 9H), 1.45−1.42 (m, 1H), 1.31 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 176.1, 146.5, 144.6, 128.3, 127.7, 127.0, 101.7, 80.5, 75.4, 64.2, 63.5, 57.0, 46.5, 36.0, 28.2, 22.8, 20.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2972 (m), 2875 (w), 1721 (s), 1584 (m), 1366 (s), 1134 (s), 765 (m), 737 (m), 700 (s). HRMS (ESI): calcd for ([M + H] $C_{21}H_{30}NO_2)^+$, 328.2271; found, 328.2277. $[\alpha]_D^{20}$ = −40.8° (*c* = 1.0, CH_2Cl_2).

*Synthesis of tert-Butyl (1R,2S)-2-((2-Bromoallyl) ((S)-1-phenylethyl)amino)cyclopent-3-ene-1-carboxylate (**71**).* *n*-Butyllithium solution (1.6 M in hexanes, 2.62 mL, 4.20 mmol, 1.5 equiv) was added dropwise to a solution of DIPA (629 μL, 4.48 mmol, 1.6 equiv) in THF (7 mL) at −78 °C. After 15 min, a solution of ester **65** (1.10 g, 2.80 mmol, 1.0 equiv) in THF (7 mL) was added via syringe to the freshly prepared lithium diisopropylamide solution at −78 °C. After 30 min, allyl bromide (483 μL, 5.59 mmol, 2.0 equiv) was added, and after further 15 min, the mixture was warmed to 0 °C. After 30 min, the mixture was diluted with saturated aqueous ammonium chloride solution (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The residue was filtered through a short pad of silica, eluting with 5% ethyl acetate in hexanes (200 mL). The filtrate was concentrated in vacuo, and the residue was used in the next step without further purification. A solution of the crude α-allylated ester (assuming 2.80 mmol) in N_2-sparged (30 min) dichloromethane (60 mL) was treated with Hoveyda−Gubbs catalyst 2nd generation (87.7 mg, 140 μmol, 5 mol %) at 23 °C, and the mixture was heated to 40 °C. After 1 h, the mixture was cooled to 23 °C and was concentrated in vacuo. The crude residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give cyclopentene **71** (816 mg, 2.01 mmol, 72%) as a yellow oil. **TLC** (20% ethyl acetate in hexanes): R_f = 0.55 (UV/$KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.41−7.38 (m, 2H), 7.32−7.28 (m, 2H), 7.24−7.20 (m, 1H), 6.11 (br s, 1H), 5.79−5.75 (m, 1H), 5.56 (br s, 1H), 5.55−5.51 (m, 1H), 4.30−4.26 (m, 1H), 4.00 (q, *J* = 6.8 Hz, 1H), 3.36 (d, *J* = 16.9 Hz, 1H), 3.28 (d, *J* = 16.9 Hz, 1H), 2.72−2.67 (m, 1H), 2.61−2.55 (m, 1H), 2.41−2.36 (m, 1H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 175.3, 144.3, 135.2, 131.9, 128.4, 127.9, 126.9, 116.9, 80.2, 69.8, 59.6, 54.8, 47.2, 36.3, 28.1, 18.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2975 (m), 2931 (w), 1720 (s), 1626 (w), 1452 (m), 1366 (s), 1144 (s), 733 (s), 699 (s). HRMS (ESI): calcd for ([M + H] $C_{21}H_{29}{}^{79}BrNO_2)^+$, 406.1376; found, 406.1351. $[\alpha]_D^{20}$ = +73.6° (*c* = 1.0, CH_2Cl_2).

*Synthesis of tert-Butyl (3aR,6R,6aS)-3-Methylene-1-((S)-1-phenylethyl)-1,2,3,3A,6,6a-hexahydrocyclopenta[b]pyrrole-6-carboxylate (**73**).* A solution of cyclopentene **71** (800 mg, 1.97 mmol, 1.0 equiv) in N_2-sparged (30 min) acetonitrile (10 mL) was sequentially treated with triphenylphosphine (104 mg, 395 μmol, 0.2 equiv), triethylamine (574 μL, 4.15 mmol, 2.1 equiv), and palladium(II) acetate (44.3 mg, 197 μmol, 0.1 equiv), and the resulting mixture was heated to 80 °C. After 2.5 h, the dark red mixture was cooled to 23 °C, and then was diluted with saturated aqueous sodium bicarbonate solution (30 mL) and diethyl ether (30 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (5% → 10% ethyl acetate in hexanes) to give diene **73** (352 mg, 1.08 mmol, 55%) as a dark red solid. **TLC** (20% ethyl acetate in hexanes): R_f = 0.44 (UV/$KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.32−7.30 (m, 4H), 7.26−7.23 (m, 1H), 5.81 (dt, *J* = 5.6, 2.2 Hz, 1H), 5.65−5.62 (m, 1H), 4.89 (br s, 1H), 4.85 (br s, 1H), 3.81−3.77 (m, 1H), 3.77−3.71 (m, 2H), 3.63−3.60 (m, 1H), 3.33 (d, *J* = 12.9 Hz, 1H), 3.01 (d, *J* = 12.8 Hz, 1H), 1.46 (s, 9H), 1.44 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 173.0, 149.3, 142.8, 134.6, 128.3, 128.0, 127.5, 127.2, 105.4, 80.8, 68.1, 62.7, 59.7, 56.9, 54.6, 28.3, 22.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (m), 2774 (w), 1721 (s), 1453 (m), 1366 (s), 1258 (m), 1137 (s), 702 (s). HRMS (ESI): calcd for ([M + H] $C_{21}H_{28}NO_2)^+$, 326.2115; found, 326.2130. $[\alpha]_D^{20}$ = +195.3 (*c* = 1.0, CH_2Cl_2). mp 45−50 °C.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b02223.

Key NOESY correlations of compounds **25**, **36**, **40**, **70**, **C8-*epi*-70**, and **73**, optimization tables, chiral HPLC analyses, proposed and revised biosynthetic pathway, and copies of NMR spectra (PDF)

Crystallographic information for compound S109 (CIF)

Crystallographic information for compound 87 (CIF)

Crystallographic information for compound 100 (CIF)

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Notes

The authors declare no competing financial interest.

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J. Org. Chem. 2019, 84, 14069−14091

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